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Accessing Fused and Spirocyclic Ring Formations via Carbon – Carbon Bond Activation

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Accessing Fused and Spirocyclic Ring Formations via Carbon – Carbon Bond Activation

by

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Thesis

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Dedication

For Constance “Thia” Christopulos

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While it is my name that appears on the title page, this thesis was made possible with the assistance of many other people. I would like to thank my advisor, Dr. Guangbin Dong, for his encyclopedic knowledge and passionate support, Dr. Tao Xu for his consistently helpful research leads and unwavering motivation, and Dr. Haye Min Ko for her enthusiasm and insights. I appreciate the effort of the staff at the Texas Coffee Traders and Double Dave's Pizzaworks for continued reliability during inevitable turmoil. Thanks are also due to Mom and Dome, Hooves, Planktooon, The Tripod, Mamba, Dumplings and Rach City, who mostly never believed in me but always supported me. No thanks are given to Dr. Alpay Dermenci.

Abstract

Accessing Fused and Spirocyclic Ring Formations via Carbon – Carbon Bond Activation

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The University of Texas at Austin, 2013

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Carbon-carbon bonds are ubiquitous in synthetic chemistry and constitute the skeletal backbone of a significant number of compounds. Utilizing transition metal mediated catalysis, a wide array of fused and spirocyclic ring systems containing diverse functionalization were accessed. These investigations provide unique ways to prepare carbon frameworks that are otherwise nontrivial to construct using classical approaches. The derivatives were rapidly accessed through optimized methods.

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Chapter 1: Carbon – Carbon Bond Activation

1.1 Introduction

In an attempt to discover ideal chemical syntheses, many efforts have focused on the direct functionalization of carbon – hydrogen (C–H) bonds present on existing molecular core structures.[1] However, the construction of these intricate, carbon-based backbones oftentimes lacks efficient or generally applicable synthetic methods. Bridged and fused ring systems, in particular, are prevalent in a variety of natural products (e.g. terpenes and alkaloids, and the selected examples shown in **Figure 1.1**) and exhibit a variety of potent biological activities.[2,3]

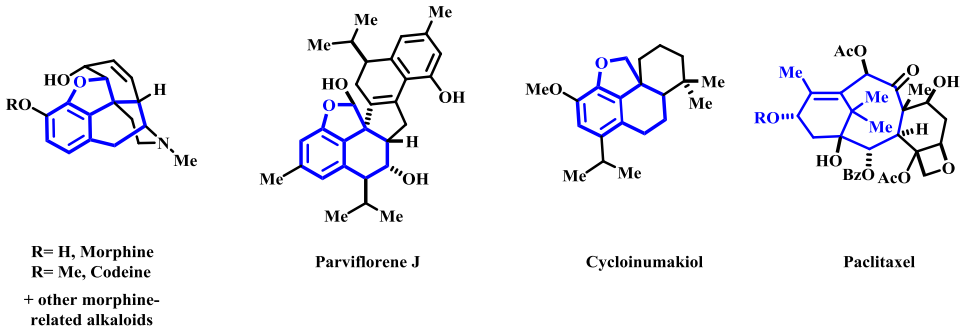


Figure 1.1 *Complex Natural Product Targets.*

The production of these rigid structures often relies upon cycloadditions or stepwise ring constructions that, although well studied, are fundamentally limited by their lengthy syntheses, specificity of reacting groups involved, and limited number of concurrent bond formations.[4,5,6] As efficiency in synthesis is a significant venture toward advancing the field of chemistry, it is of paramount importance to develop atom-

economical and selective synthetic techniques based upon carbon – carbon (C–C) bond activation of relatively inert C–C bonds and transform them into their reactive metal-carbon analogues. A method toward building complex ring systems that stems from a reliable feedstock of cheap, readily available starting materials and overcomes previous synthetic limitations is uniquely challenging and thus of principal importance, as outlined below (**Figure 1.2)**. Herein, the use of cyclic ketones as reaction precursors is proposed, which in the presence of transition metal catalysts can be preferentially "cut" open, and following migratory insertion of a pendant olefin, can be "sewn" together upon reductive elimination to afford a diverse array of new cyclized products.

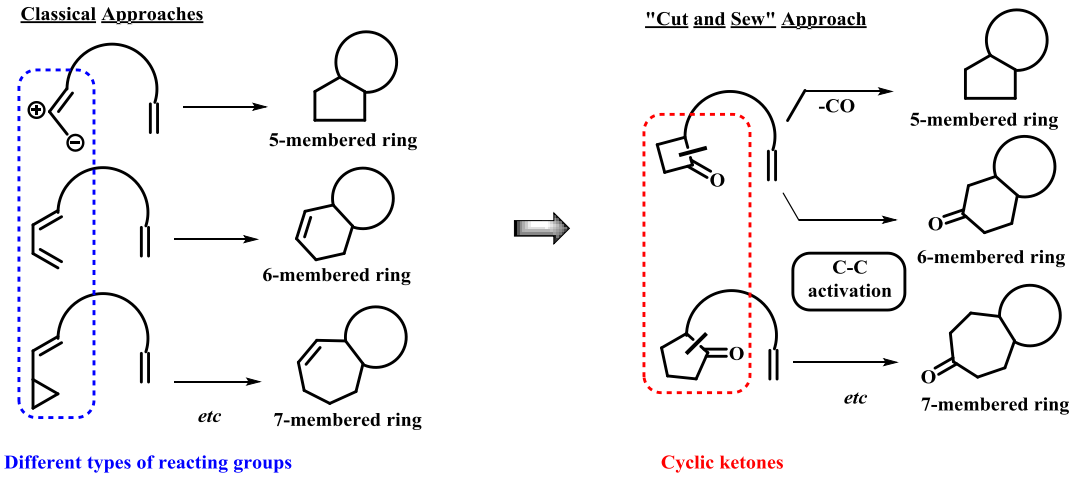


Figure 1.2 *A Unified Approach to Fused Ring Systems.*

Prior literature lends credence to the proposed research. In 1984, Liebeskind and coworkers reported the use of a stoichiometric cobalt complex to cyclize a benzocyclobutendione and a tethered alkyne.[7] Later, in 2002, Ito and Murakami illustrated the catalytic intramolecular insertion of styrene-type olefins into

cyclobutanones to afford bridged bicycles, discovering that the substrate scope was limited to mono-substituted aryl olefins (**Figure 1.3)**.[8]

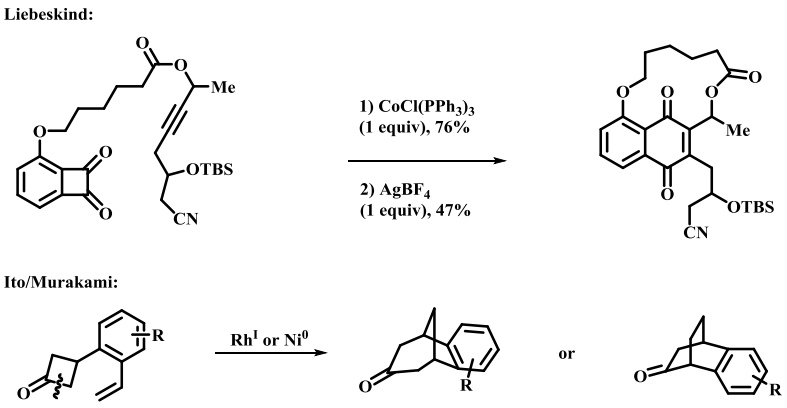


Figure 1.3 *Selected Examples of Ring Formation.*

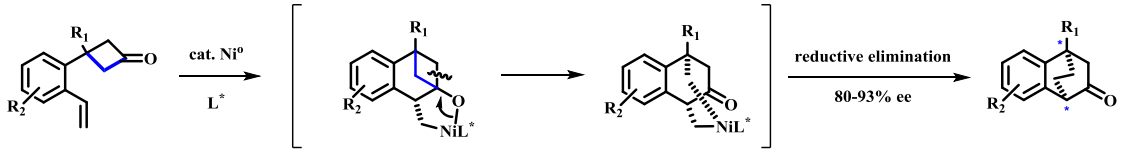
These seminal discoveries exhibited the formation of bridged-ring systems via C–C activation, but they did not further explore the scope of this reactivity. Herein, we report the investigation of new catalytic systems toward accessing fused and spirocyclic carbon-based ring systems. The research presented involves the synthesis and characterization of a wide variety of substrates that afford cyclized products dependent upon reaction conditions. The effects of both steric size and electronic substitution on catalysts, ligands, reaction additives and substrates were studied in order to discover unique modes of reactivity. With a wide array of synthetic products, further transformations were also undertaken.

Chapter 2: Efficient Synthesis of Chiral Poly-Fused Rings

(With Dr. Tao Xu and Dr. Haye Min Ko)

2.1 Introduction

Catalytic asymmetric transformations via C–C activation are significantly less studied than their C–H counterparts. Asymmetric metal-catalyzed C–C cleavage has mainly been achieved via *β*-carbon elimination of *tert*-cyclobutanolates generated *in situ* from cyclobutanolates or via deprotonation of corresponding *tert*-cyclobutanols.[9,10,11,12] Although elegant, this small sample of work suggests that metal-mediated transformations are considerably underdeveloped. In particular, the work reported recently by Murakami and coworkers is the only known example of catalytic enantioselective carboacylation of olefins (**Scheme 2.1)**.[13]



Scheme 2.1 *Catalytic Enantioselective Acylation of Olefins, Murakami.*

In their work, Murakami illustrates the nickel-mediated cyclometallation into the cyclobutanone C–C bond, which upon β-carbon elimination affords bridged-ring products. In this vein, we were interested in an effective method to access chiral fused ring systems. Based upon our recent discovery of an intramolecular olefin carboacylation with benzocyclobutanones that afforded racemic products utilizing dppb as a ligand, we investigated an enantioselective variant of this transformation.[14]

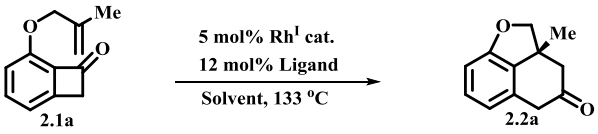
2.2 Research Objectives

In this chapter, an enantioselective rhodium-catalyzed carboacylation via a metal-insertion into benzocyclobutenone C–C bonds to access tricyclic fused rings is highlighted. These ring systems can then be further manipulated through a catalytic reductive dearomatization to afford fully saturated cyclic products. The success of this transformation, however, must first address two distinct challenges. The first is general; a larger energy difference is needed between the diastereomeric transition states at high temperatures to achieve the same level of enantioselectivity (i.e. to obtain 95% ee, $\Delta G‡$ = 12.3 kJ/mol is needed at 130 °C versus $\Delta G‡$ = 9.1 kJ/mol at r.t.). The second derives from the sensitivity of this rhodium-catalyzed reaction to the ligand employed, where discovering conditions that afford both high enantioselectivities and reactivities is nontrivial.[14] The compounds investigated were chosen for the purpose of elucidating the steric and electronic tolerance of the reaction conditions.

2.3 Results and Discussion

The synthesis of C–C activation substrates stemmed from a [2+2] coupling of derivatized benzynes and ketene acetals as detailed in later supplemental information. For early optimization studies, substrate **2.1a** was used as the model substrate. A series of rhodium-I pre-catalysts were investigated; it was ultimately determined that $[Rh(cod)Cl]_2$ was the optimal system (entries 1-4, **Table 2.1**). Based on our previous results that suggested the importance of bidentate ligands with wide bite angles to successfully enable this transformation, chiral bidentate phosphine ligands containing a four carbon linkage were firstly examined. Although BINAP and Tol-BINAP provided low yields and

enantioselectivites (entries 7 and 8), switching to DIOP provided both a good yield (73%) and ee (83%). Attempts to further enhance the enantioselectivites with bulkier DIOP ligands, afforded no improvement in ee (entries 5 and 6). In examining other bidentate ligands with axial chirality, it was discovered that the SYNPHOS class of ligands gave excellent ee, albeit with poor yields (entry 9). By switching to SEGPHOS, both yield and ee were further improved (entry 10). Increasing the electron density of the ligand was hypothesized to enhance reactivity by promoting the initial oxidative addition. Fortuitously, by utilizing DTBM-SEGPHOS, the yield was improved to 60% and upon further solvent and reaction condition investigations (entries 12-17), benzotricycle **2.2a** was obtained in 81% yield and 97% ee.



Entry	Rh^I cat	Ligand	Solvent	Yield[b]	ee[c]
1	$[Rh(C_2H_4)_2Cl]_2$	(R,R)-DIOP	THF	33% (53%)	81%
2	$[Rh(coe)_2Cl]_2$	(R,R)-DIOP	THF	55% (80%)	82%
3	$[Rh(1,5\text{-diene})Cl]_2$	(R,R)-DIOP	THF	70%	83%
4	$[Rh(cod)Cl]_2$	(R,R)-DIOP	THF	73%	83%
5	$[Rh(cod)Cl]_2$	(S,S,S,S)-DIOP	THF	10% (37%)	55%
6	$[Rh(cod)Cl]_2$	(R,S,S,R)-DIOP	THF	32% (36%)	83%
7	$[Rh(cod)Cl]_2$	(R)-BINAP	THF	12% (26%)	6%
8	$[Rh(cod)Cl]_2$	(R)-Tol-BINAP	THF	14% (42%)	11%
9	$[Rh(cod)Cl]_2$	(R)-SYNPHOS	THF	14% (27%)	94%
10	$[Rh(cod)Cl]_2$	(R)-SEGPHOS	THF	20% (28%)	97%
11	$[Rh(cod)Cl]_2$	(R)-DTBM-SEGPHOS	THF	60% (quant.)	98%
12	$[Rh(cod)Cl]_2$	(R)-DTBM-SEGPHOS	PhMe	28%	68%
13	$[Rh(cod)Cl]_2$	(R)-DTBM-SEGPHOS	DCE	0	N/A
14	$[Rh(cod)Cl]_2$	(R)-DTBM-SEGPHOS	PhCl	36%	93%
15	$[Rh(cod)Cl]_2$	(R)-DTBM-SEGPHOS	tBuOMe	43%	98%
16	$[Rh(cod)Cl]_2$	(R)-DTBM-SEGPHOS	1,4-dioxane	69%	96%
17	$[Rh(cod)Cl]_2$	(R)-DTBM-SEGPHOS	1,4-dioxane	81%[d]	97%

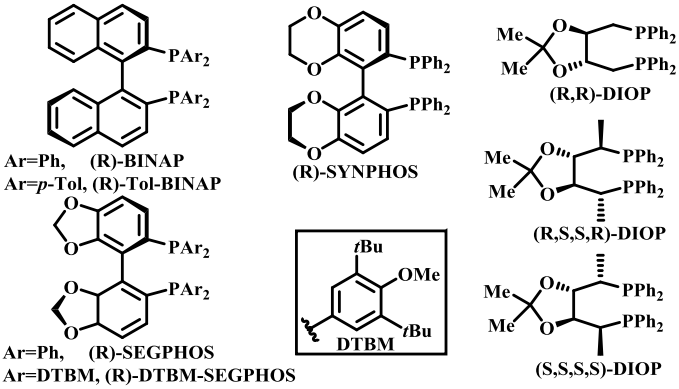


Table 2.1. *Selected Optimization of Reaction Conditions with Substrate 2.1a. (a) 5 mol % Rh precatalyst and 12 mol % ligand were used on a 0.1 mmol scale with 20h reaction time. (b) Isolated yield; numbers in parentheses are brsm yield. (c) ee was determined using chiral HPLC. (d) Reaction time was 48h.*

With the optimized reaction conditions in hand, investigations into the substrate scope of this transformation were investigated **(Table 2.2).** Delightedly, a wide variety of steric and electronic properties on a number of substrates were investigated and their products were found to have both high yields and enantioselectivities.

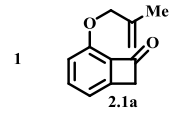
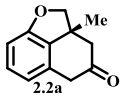
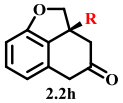
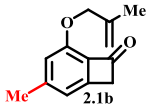
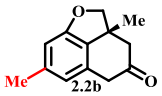
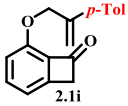
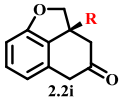
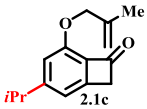
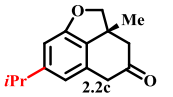
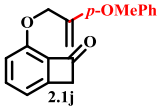
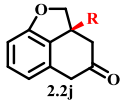
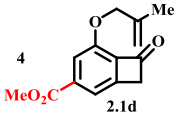
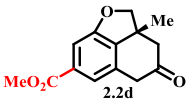
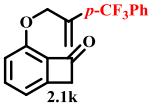
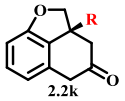
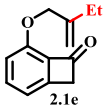
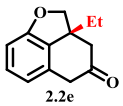
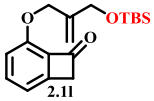
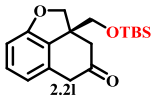
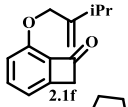
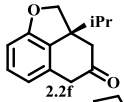
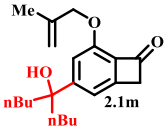
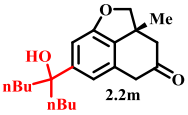
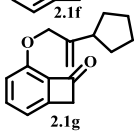
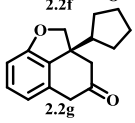
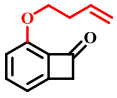
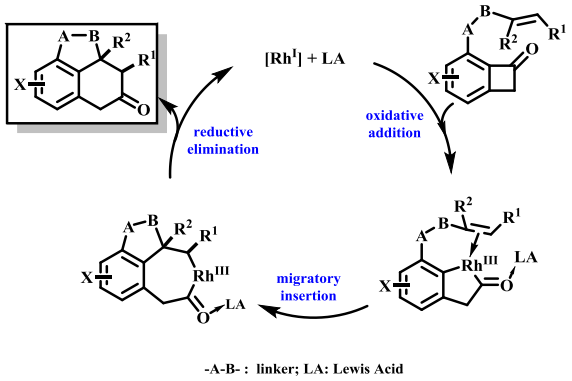
Entry	Substrate	Product	Yield[b]	ee[c]	Entry	Substrate	Product	Yield[b]	ee[c]
1	 2.1a	 2.2a	81%	97%	8	 2.1h	 2.2h	52%	96%
2	 2.1b	 2.2b	77%	98%	9[d]	 2.1i	 2.2i	76%	92%
3	 2.1c	 2.2c	74%	98%	10	 2.1j	 2.2j	55%	97%
4	 2.1d	 2.2d	61%	99%	11	 2.1k	 2.2k	47% (64%)	95%
5	 2.1e	 2.2e	65%	98%	12	 2.1l	 2.2l	53%	97%
6	 2.1f	 2.2f	44%	97%	13[d]	 2.1m	 2.2m	97%	92%
7	 2.1g	 2.2g	40%	93%	14	 2.1n	 2.2n	44% (85%)	94%

Table 2.2 *Carboacylation Substrate Scope. Reaction conditions: (a) [Rh(cod)Cl]$_2$ (5 mol %), (R)-DTBM-SEGPHOS (12 mol %), dioxane, 133 ^{0}C, 48h. (b) Isolated yield; numbers in parentheses are brsm yield. (c) ee was determined by chiral HPLC. (d) (R,R)-DIOP / THF were used instead.*

Altering the electron density of the aromatic ring had little effect on enantioselectivity, as ee's higher than 97% were observed (entries 1-4). An increase in the steric bulk of the olefin substituent decreased reactivity, but maintained high optical purities in the products formed (entries 5-7). Aryl-olefins also afforded extremely high

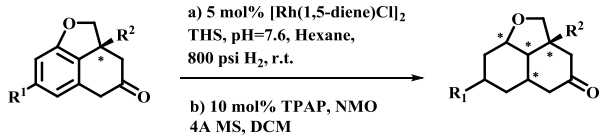
ee's and moderate yields (entries 8-11). In certain cases (entries 9 and 13), the DIOP ligand system was found to be more efficient for the transformation, increasing both yield and ee.

A proposed catalytic cycle is outlined in **Scheme 2.2.** This "cut and sew" transformation begins with the oxidative addition of rhodium-I into the benzocyclobutenone C_1–C_2 bond, which is followed by migratory insertion into the olefin to give a seven-membered metallocycle, and subsequent reductive elimination to afford the desired fused-ring systems.



Scheme 2.2 *Proposed Catalytic Cycle.*

With a wide variety of enantiomerically enriched structures in hand, it was postulated that a successful catalytic dearomatization reaction would afford fully saturated tricycles. Despite its unique elegance, the reduction of poly-substituted, electron-rich aromatic rings is challenging when compared to their unhindered and electron-deficient counterparts.[15] Nevertheless, the effective reduction to multi-substituted cyclohexanes was achieved as outlined in **Scheme 2.3**.



Scheme 2.3 *Catalytic Dearomatization.*

Excitingly, these reductions were conducted at near-neutral, room temperature conditions and afforded a stereoselective reduction on the convex face of the tricycles (likely governed by the quaternary carbon center). This caused the products to adopt a "half-cage" structure upon ensuing crystallization. In situations of over-oxidation, a Ley oxidation was implemented to ensure ketones were afforded as the sole product.[16] This reactivity provides a novel method toward accessing chiral, saturated fused ring systems.

2.4 Conclusions

A series of benzocyclobutenone derivatives were constructed with the goal of achieving insight into their ability to afford chiral fused rings under rhodium-I catalysis. Using a C–C bond activation approach with tethered olefins, the first enantioselective rhodium-catalyzed carboacylation was achieved. Isolated yields (40-97%) and excellent enantioselectivities (92-99% ee) were obtained for a number of substrates with various steric and electronic properties. Successful synthesis of fully saturated poly-fused rings was achieved using a catalytic reductive dearomatization approach, offering a unique method to prepare multiple stereocenters. These investigations provide a distinct way to prepare chiral carbo-frameworks that are nontrivial to access with conventional methods. Future work toward discovering more efficient catalyst / ligand combinations, as well as

an expansion of the substrate scope for both carboacylation and dearomatization are ongoing. In the future, this methodology may act as a new template for the strategic synthesis of terpenoid compounds.

2.5 Experimental

Instrumentation

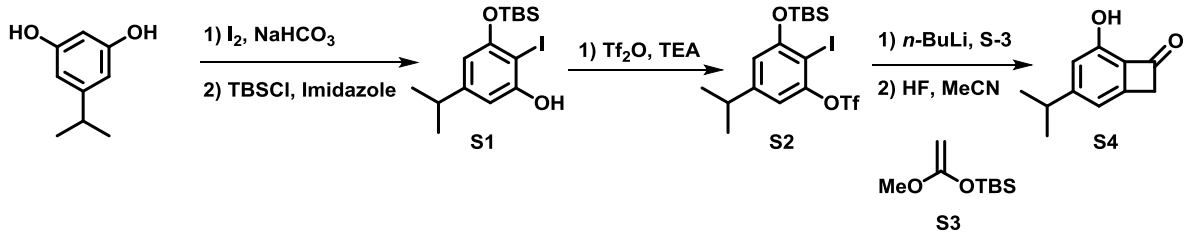
Analytical thin-layer chromatography (TLC) was carried out using 0.2 mm commercial silica gel plates (silica gel 60, F254, EMD Chemical). The vials (1 dram, 15×45 mm with PTFE lined cap attached) were purchased from Qorpak and dried in an oven overnight and cooled under a stream of nitrogen prior to use. Infrared spectra were recorded on a Nicolet 380 FTIR using a neat thin film technique. High-resolution mass spectra (HRMS) were obtained on a Karatos MS9 and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion [M+Na]+, [M+H]+, or [M+]. Nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded with a Varian Gemini (400 MHz, ^{1}H at 400 MHz, ^{13}C at 100 MHz). For $CDCl_3$ solutions the chemical shifts are reported as parts per million (ppm) referenced to residual protium or carbon of the solvents; $CHCl_3$ δ H (7.26 ppm) and $CDCl_3$ δ C (77.16 ppm). Coupling constants are reported in Hertz (Hz). Data for ^{1}H NMR spectra are reported as follows: chemical shift (ppm, referenced to protium; s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, dd = doublet of doublets, td = triplet of doublets, ddd = doublet of doublet of doublets, m = multiplet, coupling constant (Hz), and integration).

Synthesis

Unless otherwise noted, all manipulations were carried out under an inert atmosphere in a nitrogen-filled glove box or by standard Schlenk techniques. Dichloromethane (DCM), diethyl ether (Et_2O), tetrahydrofuran (THF), and toluene (PhMe) were purified using a Pure-Solv MD-5 Solvent Purification System (Innovative Technology). All other reagents were used directly from the supplier without further purification. Although in many cases the compounds listed below have been fully characterized and reported in literature, they have been included here for completeness.

Experimental Procedures and Characterization Data

Preparation of Benzocyclobutenone Structures for Carboacylation



A 250-mL, one-necked, round-bottomed flask equipped with a large, elliptical stir bar and open to the atmosphere is charged with distilled water (35 mL), THF (35 mL), 5-isopropyl-benzene-1,3-diol (3.5 g, 23 mmol) and iodine (7.49 g, 24 mmol), and then cooled in an ice-water bath.[17] To this open flask is slowly added sodium bicarbonate (2.75 g, 25 mmol) in portions by spatula over 5 minutes at 0 °C with vigorous stirring. During the addition, vigorous gas evolution (carbon dioxide) is observed. The ice bath is

removed and the mixture is allowed to warm to r.t. over 20 minutes and then stirred for another 10 minutes, during which time it becomes a brown slurry. The products are extracted with ethyl acetate (3 x 50 mL). The combined organic extracts are successively washed with 10% aqueous sodium thiosulfate solution and brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 2-iodo-5-isopropylbenzene-1,3-diol as a light yellow oil.

Imidazole (4.9 g, 72 mmol) and TBSCl (5.43 g, 36 mmol) were added to a solution of 2-iodo-benzene-1,3-diol in CH_2Cl_2 (60 mL) at 0 ^oC. This reaction mixture was stirred at r.t. for 1 hour and was quenched by the addition of H_2O (50 mL). The reaction mixture was extracted with CH_2Cl_2 (50 mL x 3) and the organic phase was washed with brine (60 mL), dried over $MgSO_4$, filtered and concentrated. Purification of the residue by flash column chromatography (hexanes:EtOAc, 2:1) provided compound **S1** (4.25 g, 65% for 2 steps). **R*f*** = 0.5 (EtOAc/Hexane = 1/2). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.53 (d, *J* = 2.0 Hz, 1H), 6.29 (d, *J* = 2.4 Hz, 1H), 5.32 (s, 1H), 2.77 (quin, *J* = 6.9 Hz, 1H), 1.20 (d, *J* = 6.8 Hz, 6H), 1.06 (s, 9H), 0.28 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 156.0, 155.5, 151.5, 109.0, 105.8, 79.3, 33.8, 25.9, 23.7, 18.4, 4.0. **IR:** *v* 3489, 2959, 2929, 1571, 1425, 1350, 1254, 1192, 1055, 833 cm^{-1}; **HRMS** calc'd. for $C_{15}H_{26}IO_2Si^+$ $[M+H]^+$: 393.0747. Found: 393.0742.

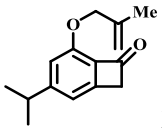
A flame-dried 200-mL Schlenk tube equipped with a magnetic stir bar, a nitrogen gas balloon and a rubber septum was charged with **S1** (1 g, 2.5 mmol) and CH_2Cl_2 (25 mL), and the mixture was cooled to –78 °C with a dry ice-acetone bath. Triethyl amine (0.43 mL, 3.0 mmol) was added by syringe. Tf_2O (0.47 mL, 2.8 mmol) was slowly added over 15 minutes via syringe while maintaining the reaction mixture at –78 °C. After

stirring for 10 minutes at –78 °C, the reaction mixture was warmed to 0 °C by replacing the dry ice-bath with an ice water bath, and stirred for 1 h. The reaction was quenched by the slow addition of aqueous ammonium chloride (20 mL), and the aqueous phase was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic extract was successively washed with saturated aqueous sodium bicarbonate solution (2 × 25 mL) and brine (2 × 25 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (hexanes-EtOAc, 5:1) provided compound **S2** (1.32 g, 98%). **R*f*** = 0.5 (EtOAc/Hexane = 1/5). **^{1}H NMR** (400 MHz, CDCl3): δ 6.77 (d, *J* = 1.6 Hz, 1H), 6.67 (d, *J* =1.2 Hz, 1H), 2.85 (quin, *J* = 6.9 Hz, 1H), 1.21 (d, *J* = 7.2 Hz, 6H), 1.05 (s, 9H), 0.29 (s, 6H). **^{13}C NMR** (100 MHz, CDCl3): δ 157.3, 151.8, 151.2, 120.3, 117.2, 115.9, 112.8, 83.0, 33.8, 25.8, 23.5, 18.4, -4.0. **IR:** *v* 2962, 2931, 1597, 1559, 1420, 1215, 1141, 1016, 807, 601 cm^{-1}; **HRMS** calc'd. for $C_{16}H_{24}F_3IO_4SSi+$ [M]+: 524.0161. Found: 524.0163.

A flame-dried, 200-mL Schlenk flask equipped with a magnetic stirrer bar, a nitrogen gas balloon and a rubber septum was charged with 3-((*tert*-butyldimethylsilyl)oxy)-2-iodo-5-isopropylphenyl trifluoromethanesulfonate (1.0 g, 1.9 mmol). The flask was flushed with nitrogen, THF (50 mL) and **S3** (0.72 mL, 3.24 mmol) were added by syringe, and the mixture was cooled to –78 °C with a dry ice-acetone bath. A solution of *n*BuLi in hexanes (2.5 M, 1.5 mL, 3.8 mmol) was added to the reaction mixture over 20 minutes via syringe. The reaction mixture was further stirred for 5 minutes at –78 °C, then water (5 mL) was added drop wise. After warming to r.t., water (40 mL) was added, and the products were extracted with ether (3 × 40 mL). The combined organic extracts were washed with brine (40 mL), dried over anhydrous

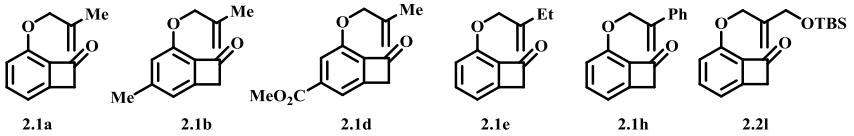
sodium sulfate, filtered, and concentrated under reduced pressure to give the crude product as a light yellow oil. This was used directly for the next step without further purification.

A 250-mL, round-bottomed flask equipped with a magnetic stirrer bar, was charged with this crude product in CH_3CN (40 mL) and the mixture was cooled to 0 °C in an ice-water bath. Aqueous HF (27.6M, 0.7 mL, 19 mmol) was slowly added during 2 minutes via syringe. The mixture was warmed to r.t. over 20 minutes, then stirred for another 13h at 40 °C. The reaction mixture was carefully poured into saturated aqueous sodium bicarbonate solution (30 mL), and the products are extracted with ethyl acetate (3 × 30 mL). The combined organic extract was successively washed with saturated aqueous sodium bicarbonate solution (30 mL) and brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a yellow oil residue. The residue was purified by column chromatography on silica gel to give 315 mg of **S4** as light yellow oil in 93% yield. **R*f*** = 0.4 (EtOAc/Hexane=1/5). **^{1}H NMR** (400 MHz, CDCl3): δ 9.25 (s, 1H), 6.89 (s, 1H), 6.67 (s, 1H), 3.84 (s, 2H), 2.90 (quin, *J* = 6.9 Hz, 1H), 1.24 (d, *J* = 6.4 Hz, 6H). **^{13}C NMR** (100 MHz, CDCl3): δ 188.3, 162.2, 150.6, 149.4, 129.8, 114.6, 113.3, 50.3, 35.3, 23.6. **IR:** *v* 3337, 2962, 2927, 1735, 1612, 1454, 1302, 1147, 1049, 853 cm^{-1}; **HRMS** calc'd. for $C_{11}H_{13}O_2$+ [M+H]+: 177.0916.
Found: 177.0910.



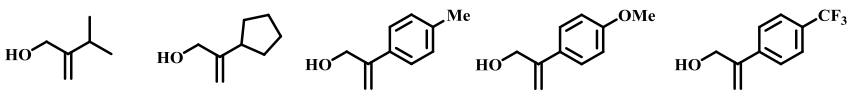
2.1c

3-chloro-2-methylprop-1-ene (0.14 mL, 1.4 mmol) was added in one portion to a solution of acetone (15 mL) containing **S4** (100 mg, 0.56 mmol), potassium carbonate (392 mg, 2.8 mmol) and potassium iodide (283 mg, 1.7 mmol). The reaction mixture was heated to reflux for overnight. Then the reaction was quenched with aqueous ammonium chloride (10 mL). The aqueous phase was extracted with ethyl acetate (2 × 10 mL) and the combined organic extract was washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a colorless residue. The residue was as purified by column chromatography on silica gel to give 120 mg (92%) of **2.1c** as colorless oil. **R*f*** = 0.6 (EtOAc/Hexane=1/5). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.89 (s, 1H), 6.72 (s, 1H), 5.05 (d, *J* = 0.8 Hz, 1H), 4.93 (d, *J* = 1.2 Hz, 1H), 4.80 (s, 2H), 3.83 (s, 2H), 2.90 (quin, *J* = 7.0 Hz, 1H), 1.82 (s, 3H), 1.24 (d, *J* = 6.8 Hz, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 184.4, 160.8, 152.5, 150.5, 140.6, 130.2, 114.4, 113.6, 112.6, 75.5, 50.6, 35.1, 23.7, 19.4. **IR:** *v* 2962, 2926, 1762, 1609, 1571, 1448, 1329 1223, 1061, 914 cm^{-1}; **HRMS** calc'd. for $C_{15}H_{19}O_2$+ [M+H]+: 231.1385. Found: 231.1385.



2.1a **2.1b** **2.1d** **2.1e** **2.1h** **2.2l**

2.1a, 2.1b, 2.1d, 2.1e, 2.1h, and **2.1l** matched the data that was reported in the literature.[18]

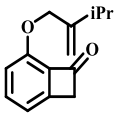


S5a **S5b** **S5c** **S5d** **S5e**

Allyl alcohols **S5a-e** are known compounds and were synthesized according to literature procedure.[19]

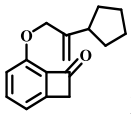
Preparation of C–C Activation Precursors for Carboacylation

A flame-dried Schlenk flask equipped with a magnetic stirrer bar was charged with benzocyclobutenone (1 equiv.), PPh_3 (1.1 equiv.), and R'CH_2OH (1.1 equiv.). The flask was degassed three times under nitrogen before THF was added via cannula. Then DIAD (1.1 eq.) was added via syringe drop wise to the solution. The reaction was heated to reflux and monitored by TLC. When the reaction was finished, it was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to yield the desired alkylation product.



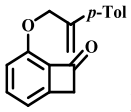
2.1f

Compound **2.1f** was isolated as a yellow oil in 98% yield from benzocyclobutenone and **S5a**. **R*f*** = 0.7 (EtOAc/Hexane=1/5). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.43 (dd, *J* = 8.4, 7.2 Hz, 1H), 7.02 (d, *J* = 7.2 Hz, 1H), 6.86 (dd, *J* = 8.4, 0.8 Hz, 1H), 5.12 (d, *J* = 1.6 Hz, 1H), 5.00 (t, *J* = 1.0 Hz, 1H), 4.91 (s, 2H), 3.92 (s, 2H), 2.46 (quin, *J* = 6.9 Hz, 1H), 1.12 (d, *J* = 6.8 Hz, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 185.0, 152.4, 150.5, 150.4, 137.7, 132.4, 116.3, 115.1, 109.9, 74.0, 51.2, 31.1, 21.6. **IR:** *v* 2962, 2928, 1769, 1604, 1574, 1474, 1275, 1129, 1052, 783 cm^{-1}; **HRMS** calc'd. for $C_{14}H_{15}O_2$ - [MH]-: 215.1072. Found: 215.1073.



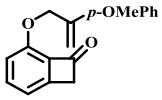
2.1g

Compound **2.1g** was isolated as a yellow oil in 93% yield from benzocyclobutenone and **S5b**. **R*f*** = 0.7 (EtOAc/Hexane=1/5). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.42 (dd, *J* = 8.6, 7.0 Hz, 1H), 7.01 (d, *J* = 7.2 Hz, 1H), 6.84 (d, *J* = 8.8 Hz, 1H), 5.10-5.09 (m, 1H), 4.99 (d, *J* = 0.8 Hz, 1H), 4.89 (s, 2H), 3.90 (s, 2H), 2.54 (quin, *J* = 8.6 Hz, 1H), 1.92-1.84 (m, 2H), 1.74-1.65 (m, 2H), 1.64-1.53 (m, 2H), 1.51-1.39 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 184.9, 152.4, 150.5, 147.8, 137.7, 132.4, 116.3, 115.1, 109.8, 74.7, 51.2, 43.3, 31.4, 24.8. **IR:** *v* 2954, 2868, 1768, 1603, 1573, 1474, 1275, 1128, 1052, 782 cm^{-1}; **HRMS** calc'd. for $C_{16}H_{19}O_2$+ [M+H]+: 243.1385. Found: 243.1385.



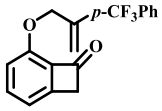
2.1i

Compound **2.1i** was isolated as a colorless oil in 89% yield from benzocyclobutenone and **S5c**. **R**f = 0.65 (EtOAc/Hexane=1/5). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.46-7.42 (m, 3H), 7.18 (d, *J* = 8.4 Hz, 2H), 7.05 (d, *J* = 6.8 Hz, 1H), 6.86 (d, *J* = 8.8 Hz, 1H), 5.59 (d, *J* = 0.8 Hz, 1H), 5.43 (dd, *J* = 2.6, 1.4 Hz, 1H), 5.31 (d, *J* = 0.8 Hz, 2H), 3.95 (s, 2H), 2.36 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 185.2, 152.3, 150.7, 142.6, 137.9, 137.8, 135.2, 132.7, 129.3, 126.0, 116.6, 115.4, 114.0, 73.9, 51.4, 21.3. **IR:** *v* 2921, 1765, 1603, 1572, 1474, 1447, 1272, 1129, 1053, 824 cm^{-1}; **HRMS** calc'd. for $C_{18}H_{17}O_2$+ [M+H]+: 265.1229. Found: 265.1223.



2.1j

Compound **2.1j** was isolated as a sticky oil in 98% yield from benzocyclobutanone and **S5d**. **R*f*** = 0.4 (EtOAc/Hexane=1/5). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.48-7.42 (m, 3H), 7.05 (dd, *J* = 7.2, 0.4 Hz,1H), 6.91-6.88 (m, 2H), 6.86 (dd, *J* = 8.4, 0.4 Hz, 1H), 5.52 (d, *J* = 0.8 Hz, 1H), 5.38 (d, *J* = 1.2 Hz, 1H), 5.29 (d, *J* = 0.8 Hz, 2H), 3.95 (d, *J* = 0.8 Hz, 2H), 3.82 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 185.1, 159.5, 152.1, 150.5, 142.0, 137.8, 132.5, 130.5, 127.2, 116.5, 115.3, 113.8, 113.0, 73.8, 55.3, 51.2. **IR:** *v* 2961, 2928, 2832, 1762, 1603, 1570, 1264, 1125, 1052, 835 cm^{-1}; **HRMS** calc'd. for $C_{18}H_{16}O_3$ [M]+: 280.1099. Found: 280.1096.



2.1k

Compound **2.1k** was isolated as a light yellow oil in 90% yield from benzocyclobutanone and **S5e**. **R**f = 0.6 (EtOAc/Hexane=1/5). **^{1}H NMR** (400 MHz, CDCl3): δ 7.65-7.60 (m, 4H), 7.45 (dd, *J* = 8.2, 7.0 Hz, 1H), 7.07 (d, *J* = 6.8 Hz, 1H), 6.85 (d, *J* = 8.8 Hz, 1H), 5.68 (d, *J* = 0.8 Hz, 1H), 5.58 (d, *J* = 0.8 Hz, 1H), 5.33 (s, 2H), 3.96 (s, 2H). **^{13}C NMR** (100 MHz, CDCl3): δ 152.0, 150.7, 141.9, 141.7, 138.0, 132.6, 129.9, 126.6, 125.6, 125.57, 125.53, 122.9, 116.9, 116.6, 115.8, 73.5, 51.4. **IR:** *v* 2987, 2359, 1770, 1603, 1574, 1475, 1328, 1121, 1069, 847 cm^{-1}. **HRMS** calc'd. for $C_{18}H_{13}O_2F_3$+ [M]+: 318.0868. Found: 318.0869.

S6 **2.1m**

S6 was synthesized from commercially available Methyl 3,5-dihydroxybenzoate in 65% overall yield according to literature. A flame-dried, 200-mL Schlenk flask equipped with a magnetic stirrer bar, a nitrogen gas balloon and a rubber septum was charged with **S6** (150 mg, 0.31 mmol). The flask was flushed with nitrogen, THF (15 mL) and **S3** (0.11 mL, 0.51 mmol) were added by syringe, and the mixture was cooled to –78 °C with a dry ice-acetone bath. A solution of *n*-BuLi in hexanes (2.5 M, 0.4 mL, 0.93 mmol) was added to the reaction mixture over 20 minutes via syringe. The reaction mixture was further stirred for 5 minutes at –78 °C, then water (5 mL) was added drop wise. After warming to r.t., water (10 mL) was added, and the products were extracted with ether (3 × 15 mL). The combined organic extract was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give the crude product as a yellow oil. This was used directly for the next step without further purification.

A 250-mL, round-bottomed flask equipped with a magnetic stirrer bar was charged with this crude product in CH_3CN (15 mL) and the mixture was cooled to 0 °C in an ice-water bath. Aqueous HF (27.6M, 0.11 mL, 3.1 mmol) was slowly added over 2 minutes via syringe. The mixture was warmed to r.t. over 20 minutes, then stirred for

another 13h at 40 °C. The reaction mixture was carefully poured into saturated aqueous sodium bicarbonate solution (15 mL), and the products are extracted with ethyl acetate (3 × 15 mL). The combined organic extract was successively washed with saturated aqueous sodium bicarbonate solution (20 mL) and brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a yellow oil residue. The residue was purified by column chromatography on silica gel to give 83 mg of **2.1m** as a yellow oil in 80% yield.

R*f* = 0.7 (EtOAc/Hexane=1/5). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.04 (s, 1H), 6.90 (s, 1H), 5.06 (s, 1H), 4.94 (s, 1H), 4.82 (s, 2H), 3.86 (s, 2H), 1.83 (s, 3H), 1.79-1.71 (m, 4H), 1.28-1.21 (m, 6H), 1.01-0.97 (m, 2H), 0.83 (t, *J* = 6.6 Hz, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 184.5, 158.5, 152.1, 150.1, 140.5, 130.4, 113.4, 112.7, 112.5, 77.5, 75.5, 50.7, 42.9, 25.5, 23.0, 19.4, 14.0. **IR:** *v* 3493, 2956, 2933, 1757, 1610, 1571, 1449, 1142, 1068, 905 cm^{-1}; **HRMS** calc'd. for $C_{21}H_{31}O_3$+ [M+H]+: 331.2273. Found: 331.2274.

Condition A for the Rh-catalyzed C−C Activation (Reactions were performed at 0.1~0.2 mmol scale and 0.1 M concentration):

In a nitrogen-filled glove box, a 1 dram vial was charged with 5 mol% $[Rh(cod)Cl]_2$ and 12 mol% (*R*,*R*)-DIOP. A solution of starting material in THF (0.1 M) was added and the 1 dram vial was capped and the solution was maintained at 133 °C for 12 h. The reaction was removed from the glove box and purified by flash chromatography.

Condition B for the Rh-catalyzed C−C Activation (Reactions were performed at 0.1~0.2 mmol scale and 0.1 M concentration):

In a nitrogen filled glove box, a 1 dram vial was charged with 5 mol% $[Rh(cod)Cl]_2$ and 12 mol% (*R*)-DTBM-SEGPHOS. A solution of starting material in dioxane (0.1 M) was added and the 1 dram vial was capped and the solution was maintained at 133 °C for 48 h. The reaction was removed from the glove box and purified by flash chromatography.

Chapter 3: Modular Catalytic Systems to Selectively Access Fused Rings

3.1 Introduction

Buoyed by the aforementioned success utilizing C–C bond activation to access fused rings, a logical extension of this work was to investigate changes in the unsaturated linkages of our model substrates. In particular, by using allenes or dienes as the migratory insertion species following the oxidative addition of rhodium into the benzocyclobutenone, subsequent reductive elimination would afford fused ring systems that retained unsaturated functionality (in the form of an olefin). Wender's work suggests the compatibility of allene substrates under rhodium-I catalysis to afford larger ring systems with inherent unsaturation.[20] Furthermore, it was postulated that by controlling a direct or decarbonylative reductive elimination a more diverse array of ring systems from unified starting materials could be accessed. This general approach, in the most basic sense, would enable access to a great diversity of medium-sized ring scaffolds difficult to access by conventional methods.

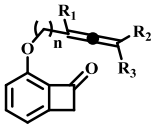
3.2 Research Objectives

It is proposed that due to the success of metal-mediated olefin insertions into benzocyclobutenones, varying the pendant unsaturated linker to include allenes or dienes will greatly expand the applicable scope of C–C activation. Herein, the aim is to further investigate various unsaturated ether-linked benzocyclobutenones and to develop a library of rhodium-mediated cyclized products that contain strategically placed

conjugation units that will enhance the inherent reactivity and functionality of the formed compounds. Studies into varying both the steric and electronic nature of substrates and catalyst/ligand system employed may lead to unique product formation and unveil mechanistic insights.

3.3 Results and Discussion

The early investigations into this portion of work studied the reactivity of allenes (whose syntheses are outlined in later supplemental information) in novel metal-mediated reactions. **Scheme 3.1** highlights the scope of reactive substrates **3.1-3.4a** investigated, whose construction stems from similar reacting partners and chemical sequences as outlined in **Chapter 2**.



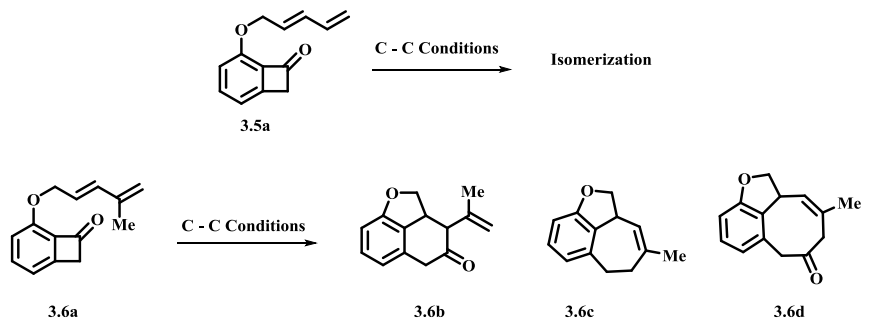
Compound	n=	R_1	R_2	R_3
(3.1a)	1	H	H	H
(3.2a)	1	Me	H	H
(3.3a)	2	H	H	H
(3.4a)	2	H	Me	Me

Scheme 3.1 *Scope of Allene Substrates Investigated.*

It was expected that our transition-metal catalyzed step would yield promising polyfused rings containing units of unsaturation, thereby expanding upon previous group precedent. Initial investigations discovered that the major products of the general reaction conditions were isomerizations of the allenes into their more favored diene products.[21] A significant thrust of work was performed using an exhaustive list of various [Rh^I] catalysts; investigations also included commercially available cationic [Rh] species. Ligands screened included general bi-dentate phosphine ligands (e.g. dppm, dppe, dppp,

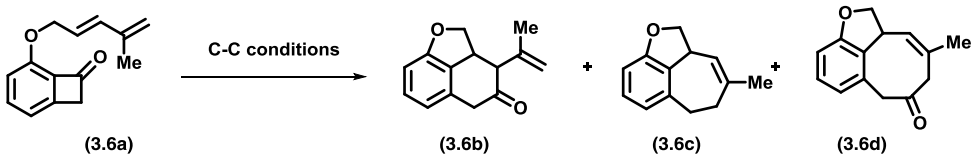
dppb), chiral bi-dentate ligands (e.g. DIOP) and mono-dentate ligands (e.g. $P(Cy)_3$, $P(C_6F_5)_3$). As evidenced by our group's precedent, the use of Lewis acids ($ZnCl_2$) was shown to activate the carbonyl moiety and aid in C–C activation. However, when tested with the allene substrates in question no additional reactivity toward fused ring formation was observed. Attempts to decrease the requisite amount of kinetic energy for this reaction by lowering the temperature to 100 ^oC also proved unsuccessful, as there was no reactivity observed, while increasing temperatures beyond 150 ^oC afforded decomposition of the starting materials. Future work will focus on the discovery and application of a new rhodium catalyst that will promote the desired C–C activation.

Inspired by the inconclusive results of the rhodium-mediated allene insertions, simple diene substrates were generated (detailed syntheses provided in supplemental information) and investigated under general C–C activation conditions as outlined in **Scheme 3.2**. While the less substituted diene compound **3.5a** afforded isomerized starting material akin to the allene investigations under a variety of reaction conditions, it was discovered that not only did compound **3.6a** afford fused-ring products; the resultant tricycles were reaction-controlled.



Scheme 3.2 *Investigations into Diene Linkages.*

It was hypothesized that the installation of an alkyl substituent, in this case a methyl group at the ∂-position of the ether functional chain, would aid in the minimization of isomerization at elevated temperatures. Thus, the model compound **3.6a** was further investigated in hopes of optimizing reaction conditions **(Table 3.1)**.



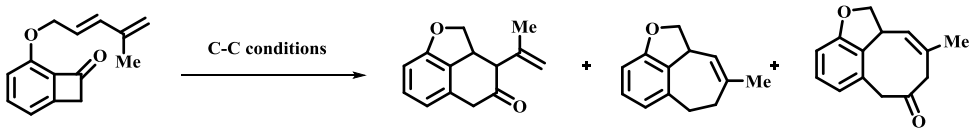
(3.6a) (3.6b) (3.6c) (3.6d)

Entry	Catalyst (5 mol%)	Additive (mol%)	Solvent	Temperature (°C)	Product
1	Wilkinson's	-	THF	133	<50% Conversion
2	$[Rh(C_2H_4)_2Cl]_2$	-	THF	133	<50% Conversion
3	$[Rh(coe)_2Cl]_2$	-	THF	133	<50% Conversion
4	$[Rh(CO)_2Cl]_2$	-	THF	133	<50% Conversion
5	$[Rh(1,5\ diene)Cl]_2$	-	THF	133	<50% Conversion
6	$[Rh(cod)Cl]_2$	(dppm - dppb) (12%)	THF	133	No Reaction
7	$[Rh(cod)Cl]_2$	dppf (12%)	THF	133	No Reaction
8	$[Rh(cod)_2BF_4]$	(dppm - dppb) (12%)	THF	133	No Reaction
9	$[Rh(cod)_2BF_4]$	dppf (12%)	THF	133	No Reaction
10	$[Rh(cod)Cl]_2$	(dppm - dppb) 12%, $ZnCl_2$ (20%)	THF	133	<10% (3.6c), <10% (3.6d)
11	$[Rh(cod)Cl]_2$	10% $AgBF_4$	THF	133	<10% Conversion
12	$[Rh(cod)Cl]_2$	-	PhMe	133	<10% Conversion
13	$[Rh(cod)Cl]_2$	-	Xylenes	133	<10% Conversion
14	$[Rh(cod)Cl]_2$	-	Dioxane	133	<10% Conversion
15	$[Rh(cod)Cl]_2$	$B(Ph)_3$ (20%)	THF	133	<10% (3.6c), <10% (3.6d)
16	$[Rh(cod)Cl]_2$	$ZnCl_2$ with BHT (20%)	THF	133	<10% (3.6c), <10% (3.6d)
17	$[Rh(cod)Cl]_2$	pyridine (100%)	THF	133	<10% (3.6c), <10% (3.6d)

Table 3.1 *Initial Optimization Conditions for Diene Cyclization.*

While by no means exhaustive, **Table 3.1** highlights some current major breakthroughs of this project. A significant amount of testing was attempted using $[Rh(cod)Cl]_2$ as the precatalyst (adapted from our previous studies on alkene activation) as it was determined to afford the best conversion of starting materials. Unfortunately, reaction additives (bidentate phosphorous ligands or otherwise) were found to significantly inhibit the formation of the desired products (in particular, the [6,5,7] fused

tricycle. After re-screening a variety of metal catalysts, an ideal catalyst system was later realized utilizing [Rh(acac)$(CO)_2$] **(Table 3.2)**.



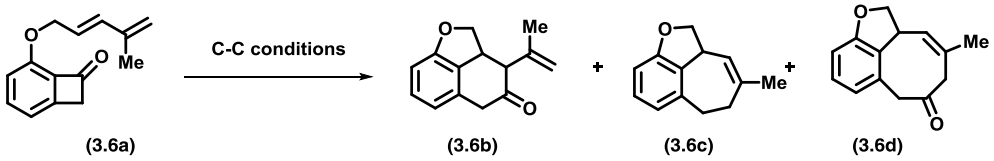
(3.6a) (3.6b) (3.6c) (3.6d)

Entry	Catalyst (5 mol%)	Additive (mol%)	Solvent	Temperature (^oC)	Product
1	$[Rh(cod)Cl]_2$	-	THF	133	10% 3.6d
2	$[Rh(1,5\ hexadiene)Cl]_2$	-	THF	133	20% Conversion
3	Ru_3CO_{12}	-	THF	133	No Reaction
4	$RuH_2(PPh_3)_4$	-	THF	133	No Reaction
5	Co_2CO_8	-	THF	133	No Reaction
6	Co_2CO_8 (50 mol%)	-	THF	133	No Reaction
7	$Rh(acac)CO_2$	-	THF	133	15% 3.6d
8	$(Rh(dppp)nbd)^+PF_6^-$	-	THF	133	No Reaction
9	$[Rh(coe)_2Cl]_2$	-	THF	133	10% 3.6d
10	$[Rh(CO)_2Cl]_2$	-	THF	133	10% 3.6d

Table 3.2 *Precatalyst Reinvestigation for Diene Cyclization.*

With the new precatalyst system in hand, a variety of reaction effects were again investigated and summarized below (**Table 3.3)**. Fortuitously, the ability to decrease the reaction temperature from 133 ^oC to 80 ^oC was most notably discovered, and this has provided a promising, if not currently limited outlook for this project. Using [Rh(acac)$(CO)_2$] allows the reaction to proceed at lower temperatures, but with longer reaction times and slightly lower conversions of the starting material. With a more optimal precatalyst system discovered utilizing acetylacetonate (acac) ligands, catalysts containing varying acac ligands were investigated and discovered to alter selectivities of compounds **(3.6b)** and **(3.6d)**, albeit decreasing the overall conversion. While this transformation is fundamentally interesting, investigations into acac-based catalyst

systems were not further studied. Unfortunately, the addition of nitrogen or phosphorous based mono- and bi-dentate ligands (with and without additional additives) often afforded conversions and yields lower than only the precatalyst system, further limiting the reaction scope. Surprisingly, certain electron deficient ligands (most notably $P(C_6F_5)_3$) facilitated reaction progression, albeit with insignificant change in product selectivity or yield. Additives such as Lewis acids or radical inhibitors, regardless of the catalyst system employed, showed decreased reactivities. Attempts to selectively foster decarbonylation products (**3.6c)** or carbonylation products (**3.6d)** (through continued argon bubbling or sealed CO pressure, respectively) proved unsuccessful. Under argon bubbling lower yields of **3.6c** were observed, while under a sealed CO atmosphere there was no evidence of reactivity, likely caused by the poisoning of the precatalyst.



(3.6a) (3.6b) (3.6c) (3.6d)

Entry	Catalyst (5 mol%)	Additive (mol%)	Solvent	Temperature (°C)	Product
1	$Rh(acac)CO_2$	-	THF	100	20% 3.6b, 25% 3.6d
2	$Rh(acac)CO_2$	-	THF	80	20% 3.6b, 40% 3.6d
3	$Rh(acac)CO_2$	-	THF	60	>75% Conversion
4	$Rh(acac)CO_2$	DMAP (100%)	THF	80	No Reaction
5	$Rh(acac)CO_2$	DMAP (5%)	THF	80	No Reaction
6	$Rh(acac)CO_2$	$ZnCl_2$ (20%)	THF	80	15% 3.6d, 25% 3.6b
7	$Rh(acac)CO_2$	Pyridine (100%)	THF	80	No Reaction
8	$Rh(acac)CO_2$	dppb	THF	80	No Reaction
9	$Rh(acac)CO_2$	dppb + $ZnCl_2$ (20%)	THF	80	No Reaction
10	$Rh(acac)CO_2$	$B(Ph_3)$ (20%)	THF	80	25% 3.6b, 25% 3.6d, 75% Conversion
11	$Rh(acac)CO_2$	Cyanopyridine (100%)	THF	80	No Reaction
12	none	-	THF	80	No Reaction
13	$[Rh(cod)Cl]_2$	-	PhMe	100	Deallylation, Isomerization
14	$[Rh(cod)Cl]_2$	-	THF	80	Deallylation, Isomerization
15	$[Rh(cod)Cl]_2$	-	THF	80	Starting Material
16	$Rh(acac)CO_2$	-	PhMe	80	70% conversion
17	$Rh(acac)CO_2$	-	DCE	80	75% conversion
18	$Rh(acac)CO_2$	-	PhCl	80	45% conversion
19	$Rh(acac)CO_2$	-	Xylenes	80	60% conversion

Table 3.3 *Selected Optimization Conditions for Diene Cyclization.*

To further investigate the scope of this transformation, a variety of polyfused rings were synthesized (detailed in supplemental information) and the results of the reactions are highlighted in **Table 3.4.**

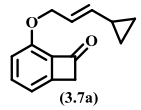
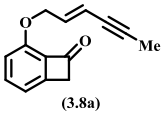
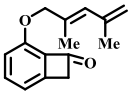
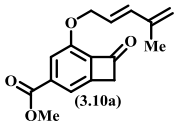
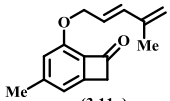
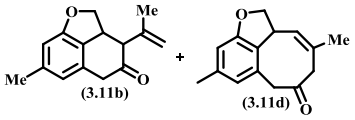
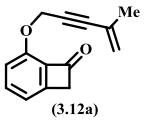
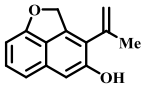
Entry	Substrate	Products	Conditions	Result
1	 (3.7a)	Trace New Compounds	5 mol% $Rh(acac)(CO)_2$ 80 °C, THF, 2 days	50% conversion
2	 (3.8a)	-----	5 mol% $Rh(acac)(CO)_2$ 80 °C, THF, 12% ligand 2 days	No Reaction
3	 (3.9a)	-----	5 mol% $Rh(acac)(CO)_2$ 80 °C, THF, 2 days	No Reaction
4	 (3.10a)	-----	5 mol% $Rh(acac)(CO)_2$ 80 °C, THF, 2 days	8% isomerization
5	 (3.11a)	 (3.11b) + (3.11d)	5 mol% $Rh(acac)(CO)_2$ 80 °C, THF, 2 days	20% (3.11b), 20% (3.11c) 40% conversion
6	 (3.12a)	 (3.12b)	5% $[Rh(cod)Cl]_2$, 12% dppb 133 °C, THF, 1 day	30% (3.12b)

Table 3.4 *Selected Expansion of the Substrate Scope.*

Unfortunately, while these are promising results toward an assortment of functionalized molecules, the modifications required for the rhodium-mediated key step underscore that the process is currently not universal, as the results outlined above arise from different catalysts and ligands on a case by case basis. These results therefore reinforce the importance of further optimizing the current varied reaction conditions into a unified method.

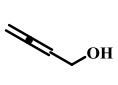
3.4 Conclusions

The preliminary work on allene and diene containing benzocyclobutenone derivatives displayed the ability to selectively cleave carbon-carbon bonds in order to construct a diverse array of polyfused ring systems from a single unified starting material. C–C activation was discovered to occur at significantly milder reaction conditions than previously reported.[14] Future work in this chapter will focus on both the continued optimization of reaction conditions and the expansion of the substrate scope for C–C activation; in particular, the versatility afforded by diversifying the unsaturated substrates tethered to the benzocyclobutenone backbone. Likewise, a detailed study into enantioselective ring formations, expansion to cheaper transition metals (e.g. cobalt), even milder reaction conditions, and a practical application to a class of natural products are all viable directions for this unique methodology.

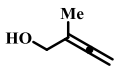
3.5 Experimental

Preparation of Allene and Diene Substrates for Fused Ring Formation

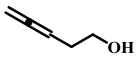
Allene alcohols **S6a-d** are known compounds and were synthesized according to literature procedure.[22,23,24]



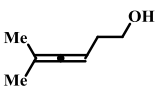
S6a



S6b

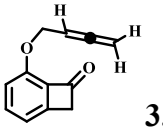


S6c



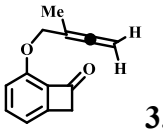
S6d

A flame-dried Schlenk flask equipped with a magnetic stirrer bar was charged with benzocyclobutenone (1.0 mmol, 1 equiv.), PPh_3 (1.1 equiv.), and **S6** (1.1 equiv.). The flask was degassed three times under nitrogen before THF (0.1 M, 10 mL) was added via cannula. Then DIAD (1.1 eq.) was added via syringe drop wise to the solution. The reaction was heated to reflux and monitored to completion by TLC (1-12 h). When the reaction was finished, it was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to yield the desired allene alkylation product.



3.1a

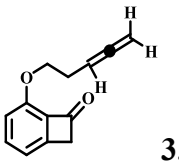
3.1a was isolated as a yellow oil in 72% yield. $\mathbf{R_f}$=0.73 (1/1 Pentanes/Et_2O). **^{1}H NMR** ($CDCl_3$, 400 MHz) 7.41 (t, *J*=8 Hz, 1H), 7.02 (d, *J*=8 Hz, 1H), 6.82 (d, *J*=8 Hz, 1H), 5.43-5.36 (m, 1H), 4.92-4.89 (m, 2H), 4.85-4.82 (m, 2H), 3.91 (s, 2H). **^{13}C NMR** ($CDCl_3$, 101 MHz) 210, 185, 152, 151, 138, 132, 116, 115, 87, 70, 51, 30.



3.2a

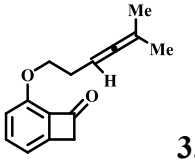
3.2a was was isolated as a pale yellow oil in 45% yield. $\mathbf{R_f}$ = 0.70 (4/1 Hexanes/EtOAc). **IR** 2926, 2860, 2333, 1765, 1457 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 400 MHz) 7.42 (t, *J*= 8 Hz, 1H) 7.02 (d, *J*= 8 Hz, 1H) 6.86 (d, *J*=8 Hz, 1H), 5.35 (d, *J*=8 Hz, 2H), 5.21 (s, 1H), 5.07

(d, *J*= 8 Hz, 3H), 3.92 (s, 2H), 2.31 (q, *J*= 8 Hz, 2H), 1.09 (t, *J*=8 Hz, 3H). **^{13}C NMR** ($CDCl_3$, 101 MHz). . **HRMS** for $C_{15}H_{16}O_2$ Calc'd 228.1 Found 228.1149.



3.3a

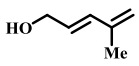
3.3a was isolated as a yellow oil in 60 % yield. **R_f**=0.70 (1/1 Pentanes/Et_2O). **^{1}H** NMR ($CDCl_3$, 400 MHz) 7.40 (t, *J*=8 Hz, 1H), 6.99 (d, *J*=8 Hz, 1H), 6.78 (d, *J*=8 Hz, 1H), 5.22-5.15 (m, 1H), 4.69 (q, 2H), 4.43 (t, 2H), 3.89 (s, 2H), 2.50-2.43 (m, 2H). **^{13}C NMR** ($CDCl_3$, 101 MHz) 209, 185, 152, 151, 138, 132, 116, 115, 86, 75, 71, 51, 29.



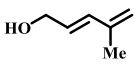
3.4a

3.4a was isolated as a pale yellow oil in 66% yield. **R_f**=0.68 (4/1 Hexanes/EtOAc) **IR** 2973, 2918, 2845, 1760, 1597, 1570, 1454, 1275 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 400 MHz) 7.40 (t, *J*=8 Hz, 1H), 6.98 (d, *J*=8 Hz, 1H), 6.78 (d, *J*=8 Hz, 1H), 5.02-4.99 (m, 1H), 4.43 (t, *J*= 8 Hz, 2H), 3.89 (s, 2H), 2.40 (q, *J*= 8 Hz, 2H), 1.64 (s, 6H). **^{13}C NMR** ($CDCl_3$, 101 MHz) 185, 153, 151, 137, 132, 116, 115, 96, 85, 72, 51, 30, 20.

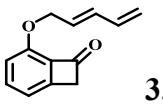
Compounds 3.5a and 3.6a were prepared in identical fashion to compounds 3.1-4a using literature known diene alcohols S7a and S7b as precursors (*vide supra*).[25,26]



S7a

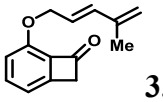


S7b



3.5a

3.5a was isolated as an amorphous white solid in 66% yield. $\mathbf{R_f}$=0.68 (4/1 Hexanes/EtOAc). **^{1}H NMR** ($CDCl_3$, 400 MHz) 7.40 (t, *J*= 8 Hz, 1H) 6.99 (d, *J*= 8 Hz, 1H) 6.80 (d, *J*=8 Hz, 1H), 6.40-6.29 (m, 2H) 5.94-5.84 (m, 1H), 5.24 (d, *J*= 16 Hz, 1H), 5.12 (d, *J*=8 Hz, 1H), 4.94 (d, *J*=8 Hz, 2H), 3.91 (s, 2H). **^{13}C NMR** ($CDCl_3$, 101 MHz) 185, 150, 138, 136, 134, 126, 119, 116, 115, 114, 113, 72, 51. **HRMS** for $C_{13}H_{12}O$ Calc'd 200.10 Found 200.0837

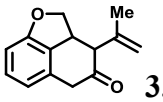


3.6a

3.6a was isolated as an amorphous yellow solid in 83% yield. $\mathbf{R_f}$=0.58 (4/1 Hexanes/EtOAc). **^{1}H NMR** ($CDCl_3$, 400 MHz) 7.42 (t, *J*= 8 Hz, 1H) 7.01 (d, *J*= 8 Hz, 1H) 6.83 (d, *J*=8 Hz, 1H), 6.47 (d, *J*=16 Hz, 1H), 5.87-5.80 (m, 1H), 5.01 (s, 2H), 4.97 (d, *J*= 8 Hz, 2H) 3.91 (s, 2H), 1.85 (s, 3H). **^{13}C NMR** ($CDCl_3$, 101 MHz). 185, 152, 150, 151, 137, 132, 123, 118, 116, 115, 114, 72, 50, 18. **IR** 3077, 2918, 1764, 1605, 1566, 1446, 1268, 1047 cm^{-1}. **HRMS** for $C_{14}H_{14}O_2$ Calc'd 214.10 Found 214.0993.

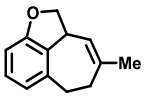
Condition A for the Rh-catalyzed C−C Activation (Reactions were performed at 0.1~0.2 mmol scale and 0.1 M concentration):

In a nitrogen-filled glove box, a 1 dram vial was charged with 5 mol% [Rh(acac)$(CO)_2$]. A solution of starting material in THF (0.1 M) was added and the 1 dram vial was capped and the solution was maintained at 133 °C for 12 h. The reaction was removed from the glove box and purified by flash column chromatography.



3.6b

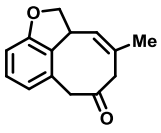
3.6b was isolated as a pale yellow oil in 25% yield. **^{1}H NMR** ($CDCl_3$, 400 MHz) 7.13 (t, *J*= 8 Hz, 1H) 6.69 (d, *J*= 4 Hz,2H), 5.05 (s, 1H) 4.80 (dd, *J*= 4Hz, 2H), 4.16 (t, *J*= 8 Hz, 1H), 3.91 (q, *J*= 8 Hz, 1H) 3.60 (d, *J*= 8 Hz, 2H), 3.01 (d, *J*= 8 Hz, 1H), 1.78 (d, *J*= 1 Hz, 3H). **^{13}C NMR** ($CDCl_3$, 101 MHz) 208, 159,, 140, 131, 130, 127, 119, 116, 107, 78, 62, 42, 40, 20.



3.6c

3.6c was isolated as a pale yellow oil in 10% yield. **^{1}H NMR** ($CDCl_3$, 400 MHz) 7.13 (t, *J*= 4 Hz, 1H) 6.48 (d, *J*= 1 Hz, 2H), 5.35 (s, 1H) 4.80 (q, *J*= 8Hz, 1H), 4.39 (bt, 1H), 4.10 (q, *J*= 8 Hz, 1H) 3.03-2.97 (m, 1H) 2.99-2.93 (m, 1H) 2.66-2.59 (m, 1H) 2.38-2.36

(m, 1H) 1.75 (s, 3H). **^{13}C NMR** ($CDCl_3$, 101 MHz) 159, 139, 138, 138, 125, 123, 121, 108, 77, 40, 32, 30, 26.

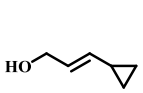


3.6d

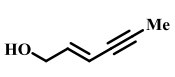
3.6d was isolated as a pale yellow oil in 16% yield. **R_f** =0.17 (5/1 Hexanes/EtOAc) **^{1}H NMR** ($CDCl_3$, 400 MHz) 7.07 (t, *J*= 6 Hz, 1H) 6.73 (d, *J*= 4 Hz, 1H), 6.66 (d, *J*= 4 Hz, 1H) 5.47 (dd, *J*= 8Hz, 1H), 4.77 (t, *J*= 10 Hz, 1H), 4.31 (t, *J*= 10 Hz, 1H) 4.22 (q, *J*= 1 Hz, 1H), 3.92 (d, *J*= 8 Hz, 1H), 3.69 (d, *J*= 8 Hz, 1H), 3.26 (d, *J*= 12 Hz, 1H), 3.15 (d, *J*= 12 Hz, 1H), 1.89 (s, 3H). **^{13}C NMR** ($CDCl_3$, 101 MHz) 207, 160, 133, 132, 129, 127, 126, 122, 109, 48, 47, 42, 30, 26. **IR** 2918, 2841, 1984, 1702, 1582, 1446, 1241 cm^{-1} **HRMS** for $C_{14}H_{14}O_2$ Calc'd 214.10 Found 214.0994.

Synthesis of Compounds 3.7a-2.12a

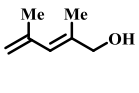
Alcohols **S8a-d** are known compounds and were synthesized according to literature procedure.[27,28,29,30] Together with the literature known diene alcohol **S7a**, these compounds were coupled to benzocyclobutenone following similar procedures previously outlined *vide supra).*



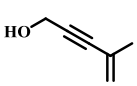
S8a



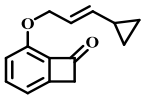
S8b



S8c

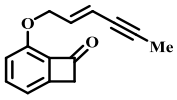


S8d



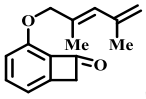
3.7a

3.7a was synthesized from **S8a** and benzocyclobutanone and was isolated as a pale yellow oil in 90% yield. $\mathbf{R_f}$ = 0.59 (4/1 Hexanes/EtOAc). **^{1}H NMR** ($CDCl_3$, 400 MHz) 7.40 (t, *J*= 8 Hz, 1H) 6.98 (d, *J*= 8 Hz, 1H) 6.81 (d, *J*=8 Hz, 1H), 4.20 (d, $_J$=1 Hz, 2H), 3.87 (s, 2H) 1.27-1.23 (m, 1H), 0.62-0.60 (m, 2H), 0.39-0.37 (m, 2H). **^{13}C NMR** ($CDCl_3$, 101 MHz). 185, 152, 150, 137, 132, 116, 115, 55, 51, 10, 3. **IR** 3074, 3004, 2922, 1764, 1601, 1566, 1469 cm^{-1}. **HRMS** for $C_{12}H_{12}O_2$ Calc'd 188.0837 Found 188.0839.



3.8a

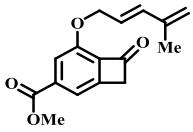
3.8a was synthesized from **S8b** and benzocyclobutanone and was isolated as a pale yellow oil in 75% yield. $\mathbf{R_f}$=0.39 (5/1 Hexanes/EtOAc). **^{1}H NMR** ($CDCl_3$, 400 MHz) 7.39 (t, *J*= 8 Hz, 1H) 6.98 (d, *J*= 8 Hz, 1H), 6.78 (d, *J*= 8 Hz, 1H) 6.15-6.11 (m, 1H), 5.77 (d, *J*= 8 Hz, 1H), 4.89 (d, *J*= 4 Hz, 2H) 3.87 (s, 2H), 1.90 (s, 3H) **^{13}C NMR** ($CDCl_3$, 101 MHz). 185, 152, 150, 137, 135, 132, 116, 115, 113, 87, 71, 69, 51, 4. **IR** 2027, 2920, 2842, 2223, 1760, 1599 cm^{-1}. **HRMS** for $C_{14}H_{12}O_2$ Calc'd 212.1 Found 211.0759.



3.9a

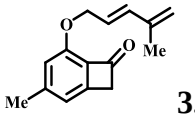
3.9a was synthesized from **S8c** and benzocyclobutanone and was isolated as an amorphous white solid in 91% yield. $\mathbf{R_f}$=0.50 (5/1 Hexanes/EtOAc). **^{1}H NMR** ($CDCl_3$,

400 MHz) 7.42 (t, *J*= 8 Hz, 1H) 7.01 (d, *J*= 4 Hz, 1H), 6.84 (d, *J*= 8 Hz, 1H) 6.00 (s, 1H), t5.00 (s 1H), 4.83 (d, *J*= 8 Hz, 3H) 3.90 (s, 2H), 1.90 (s, 3H) 1.85 (s, 3H). **^{13}C NMR** ($CDCl_3$, 101 MHz). 185, 152, 150, 141, 138, 132, 130, 116, 115, 114, 78, 51, 22, 15. **IR** 3077, 2965, 2926, 2852, 1760, 1601 cm^{-1}. **HRMS** for $C_{15}H_{16}O_2$ (M+Na)+ Calc'd 228.1 Found 251.1036.



3.10a

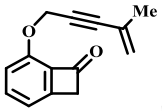
3.10a was synthesized from **S7a** and benzocyclobutanone and was isolated as a clear oil in 31% yield. **R_f**=0.55 (5/1 Hexanes/EtOAc). **^{1}H NMR** ($CDCl_3$, 400 MHz) 7.43 (t, *J*= 4 Hz, 1H) 7.01 (d, *J*= 4 Hz, 1H) 6.85 (d, *J*=8 Hz, 1H), 6.49 (d, *J*=16 Hz, 1H), 5.88-5.84 (m, 1H), 5.01 (s, 2H), 4.99 (d, *J*= 8 Hz, 1H) 4.19 (q, *J*= 8 Hz, 1H), 1.87 (s, 3H).1.45 (d, *J*= 8 Hz, 3H) **^{13}C NMR** ($CDCl_3$, 101 MHz). 189, 157, 152, 141, 136, 130, 124, 117, 116, 114, 72, 58, 18, 15. **IR** 3084, 2962, 2925, 2867, 1757, 1603, 1270 cm^{-1}. **HRMS** for $C_{15}H_{16}O_2$ Calc'd 228.1 Found 228.1150.



3.11a

3.11a was synthesized from **S7a** and benzocyclobutanone and was isolated as a clear oil in 76% yield. **R_f**=0.39 (5/1 Hexanes/EtOAc). **^{1}H NMR** ($CDCl_3$, 400 MHz) 6.85 (s, 1H) 6.66 (s, 1H), 6.48 (d, *J*= 8 Hz, 1H) 5.86-5.82 (m, 1H), 5.02 (s, 2H), 4.96 (d, *J*= 8 Hz,

2H), 3.85 (s, 2H) 2.37 (s, 3H) 1.86 (s, 3H). **^{13}C NMR** ($CDCl_3$, 101 MHz). 185, 152, 150, 149, 141, 136, 130, 123, 117, 116, 116, 72, 50, 22, 18. **IR** 3081, 2922, 1806, 1756, 1617, 1570, 1283 cm^{-1}. **HRMS** for $C_{15}H_{16}O_2$ (M+Na)+ Calc'd 228.1 Found 251.1039



3.12a

3.12a was synthesized from **S8d** and benzocyclobutanone and was isolated as a pale yellow oil in 77% yield. **R_f**=0.60 (5/1 Hexanes/EtOAc). **^{1}H NMR** ($CDCl_3$, 400 MHz) 7.44 (t, *J*= 8 Hz, 1H) 7.05 (d, *J*= 8 Hz, 1H), 6.86 (d, *J*= 8 Hz, 1H) 5.27 (d, *J*=24 Hz, 2H), 5.14 (s, 2H) 3.92 (s, 2H), 1.86 (s, 3H). **^{13}C NMR** ($CDCl_3$, 101 MHz). 185, 151, 150, 137, 132, 123, 116, 115, 88, 82, 60, 51, 23. **IR** 2922, 1765, 1602, 1575, 1474, 1269 cm^{-1}. **HRMS** for $C_{14}H_{12}O_2$ (M+Na)+ Calc'd 212.1 Found 235.0629.

Chapter 4: Decarbonylative Coupling to Access Functionalized Spirocycles

(With Dr. Tao Xu)

4.1 Introduction

As previously evidenced, catalytic C–C activation and subsequent functionalization provides a unique method toward developing complex structures that are otherwise non-trivial to access. In this creative vein, C–C activation that would involve a decarbonylative process is of significant synthetic value because it allows for the formation of compounds lacking a carbonyl moiety from their more readily available ketone precursors.[31] Nevertheless, this decarbonylative sequence has heretofore been limited in its reaction scope, using either of the two generally established methods exhibited below: the direct extrusion of CO to afford hydrocarbon products or the coupling with extremely simple olefin partners and subsequent CO elimination **(Figure 4.1)**.[32,33]

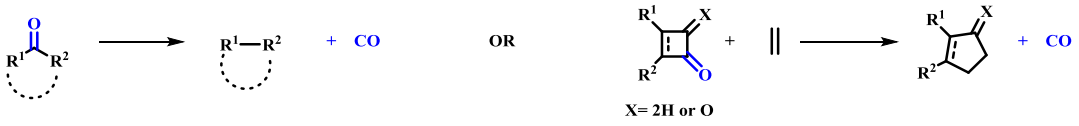


Figure 4.1 *C–C Activation via Decarbonylation.*

The discovery of novel, synthetically useful transformations is thusly of great importance. Given the ubiquity of carbonyl compounds in synthesis, these transformations would create a unique synthetic sequence that results in the removal of

carbonyl groups upon the formation of desired products. Based upon our recent developments of the intramolecular carboacylation between benzocyclobutenones and olefins (namely the oxidative addition of rhodium-I into the benzocyclobutenone C_1–C_2 bond, followed by migratory insertion into a tethered olefin and subsequent reductive elimination to afford fused-ring systems) it was postulated if a β-H elimination/ decarbonylation sequence could be preferentially promoted to construct spirocyclic systems. Given that spirocycles are important structural motifs often found in bioactive natural products (**Figure 4.2**), and that efficient synthesis of functionalized spirocycles is challenging, this decarbonylative C–C activation strategy would provide a complementary approach to the previous spirocyclization methods.[34,35]

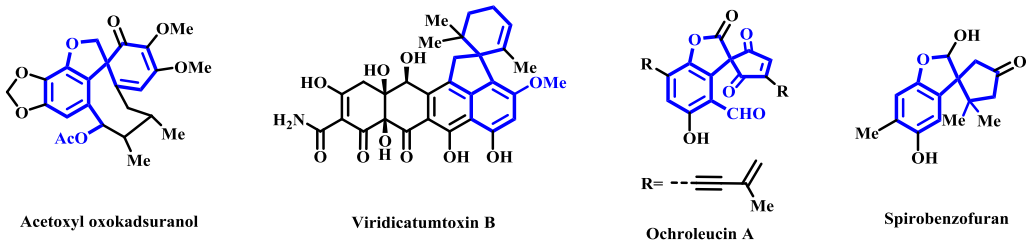


Figure 4.2 *Representative Spirocyclic Natural Products.*

4.2 Research Objectives

In this chapter, we outline our development of a rhodium-catalyzed decarbonylative spirocyclization via an intramolecular coupling between multi-substituted olefins and benzocyclobutenones by combining C–C activation, pendant olefin insertion, β-H elimination and CO extrusion in one catalytic cycle. The greatest challenge was the preferential β-H elimination and subsequent decarbonylation sequence

over reductive elimination, a challenge that was overcome by utilizing an ideal catalyst and ligand system **(Figure 4.3).**

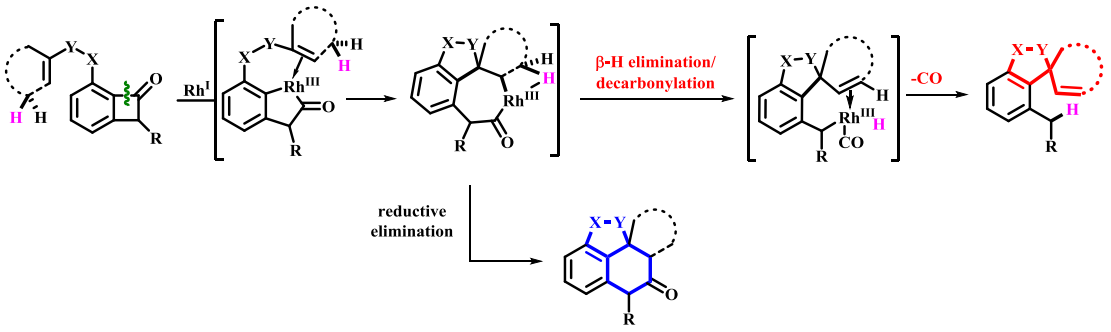
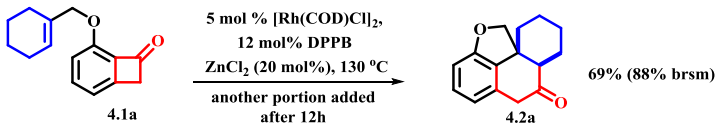


Figure 4.3 *Selective Product Formation.*

Encouraged by the recent work of Tang, it was hypothesized that the use of π-acidic ligands would benefit spirocycle formation.[36] Two explanations for the reactivity the Tang group observed involve the faster ligand exchange (compared to their bidentate counterparts) that was exhibited by monodentate phosphine ligands to facilitate the formation of a greater number of open coordination sites present on the rhodium metal (which favors both β-H elimination and CO deinsertion) and the use of a more electron-deficient catalyst that exhibits stronger coordination with multisubstituted olefins that facilitates migratory insertion.[37]

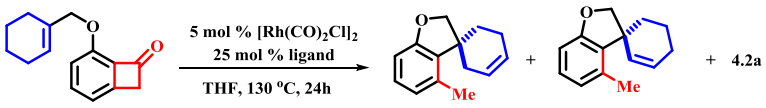
4.3 Results and Discussion

We began our investigations with model compound **4.1a**, a compound that under previous reaction conditions afforded fused ring product **4.2a (Scheme 4.1).**



Scheme 4.1 *Previous Tri-Substituted Olefin Insertion Results.*

Under the initial investigations of rhodium-I precatalysts and phosphine ligands **(Table 4.1)**, it was discovered that when electron-rich or bidentate ligands (such as PCy_3 or dppb), were employed, no desired decarbonylative spirocyclization product was obtained. More electron-deficient catalysts, on the contrary, afforded compound **4.3a** in 3% yield (entry 1). Use of an acac ligand on the rhodium in place of a chloride was found to be detrimental to the catalyst reactivity, leading to slight decomposition of **4.1a** (entry 2). The *in situ* generated cationic rhodium-I led to the dealkylation of **4.1a** to give 3-OH-benzocyclobutenone (entry 3). Use of the more electron-rich PPh_3 or highly electron-deficient phosphites as ligands completely shut down catalyst reactivity (entries 4-6).



4.1a 4.3a 4.4a

Entry	Precatalyst	Ligand/Additive	Yield 4.3a/4.4a	Yield 4.2a
1	$[Rh(CO)_2Cl]_2$	none	3%/0%	2%
2[b]	$Rh(CO)_2acac$	none	0%	0%
3[c]	$[Rh(CO)_2Cl]_2$	10 mol % $AgSbF_6$	0%	0%
4	$[Rh(CO)_2Cl]_2$	PPh_3	0%	0%
5	$[Rh(CO)_2Cl]_2$	$P(OCH_2CF_3)_3$	0%	0%
6	$[Rh(CO)_2Cl]_2$	$P[OCH(CF_3)_2]_3$	0%	0%
7	$[Rh(CO)_2Cl]_2$	P(2-furyl)$_3$	7%/4%	22%
8	$[Rh(CO)_2Cl]_2$	$P[3,5\text{-}(CF_3)_2C_6H_3]_3$	14%/14%	39%
9[d]	$[Rh(CO)_2Cl]_2$	$P(C_6F_5)_3$	30%/7%	60%
10[d,e]	$[Rh(CO)_2Cl]_2$	10 mol% $P(C_6F_5)_3$	72%[f]/0%	22%

Table 4.1 *Selected Optimization Conditions with Compound **4.1a** (a) Yields were determined by ^{1}H-NMR using mesitylene as the internal standard. (b) 10 mol % $Rh(CO)_2(acac)$ was used. (c) 3-OH-benzocyclobutenone was isolated in 53% yield. (d) The reaction time was 36 h. (e) 10 mol % $P(C_6F_5)_3$ ligand was used. (f) Isolated yield.*

Strikingly, the use of π-acidic triarylphosphine ligands significantly promoted formation of the desired spirocycle **4.3a** (entries 7-11, **Table 4.1**), among which the $P(C_6F_5)_3$ ligand proved to be most efficient. By simply lowering the ligand:metal ratio to 1:1, formation of the undesired reductive-elimination product (**4.2a**) was significantly inhibited; spirocycle **4.3a** was isolated as the major product in a 72% yield (entry 10). It is presumed that in the presence of less ligand, the rhodium metal has a larger number of open coordination sites for β-H elimination.

With the optimized reaction conditions in hand, the scope of this decarbonylative spirocyclization was investigated **(Table 4.2)**. Upon the examination of cyclic olefins with various ring sizes, it was discovered that a wide variety of ring substrates smoothly underwent this transformation (entries 1-5) with almost a single olefin isomer observed in each case. In the case of substrate **4.1e**, the product afforded was a *trans* olefin in high yield likely caused by a transannular interaction introduced by the dodecacycle.[38]

Electron deficient substrates, dienes, enamides, and benzyl and vinyl ethers were all shown to undergo this transformation with varying success. The relatively neutral nature of this reaction system is believed to prevent the degradation of sensitive functionalities. Interestingly, with the exception of substrates **4.1a, 4.1i** and **4.1m**, no direct reductive elimination products were observed for the other substrates depicted in **Table 4.2**. It is also interesting to find that the C_5-methyl-substituted benzocyclobutenone **4.1m** showed high reactivity, whereas further substitution or functionalization at this position lead to sluggish product formations.

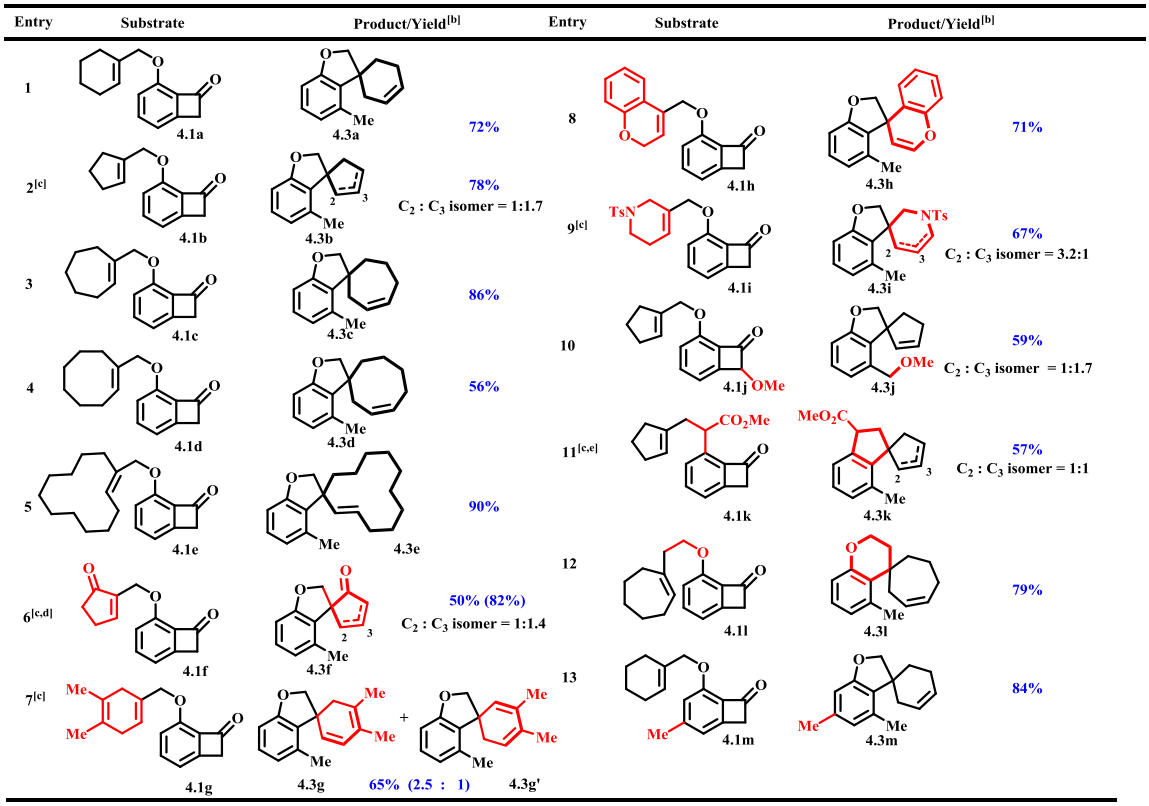


Table 4.2 *Spirocyclization Substrate Scope. (a) Reactions were run on a 0.2 mmol scale using 5 mol % $[Rh(CO)_2Cl]_2$ and 10 mol % $P(C_6F_5)_3$, in THF, 130 °C, 36 h. (b) Isolated yields. (c) Ratios of olefin regioisomers were determined by ^{1}H-NMR or based on their isolated yields (see supporting information for more details). (d) Numbers in the parenthesis are based on recovered starting material yields. (e) Compound **4.3k** was characterized via a subsequent olefin hydrogenation (see supporting information for more details).*

Further investigations not performed by the author provided mechanistic insights into this transformation. Following a deuterium-labeling experiment, compound **4.1n** underwent spirocyclization to afford spirocycle **4.3n** with >95% deuterium incorporation at the methyl substituent with an overall yield of 79% **(Figure 4.4).**

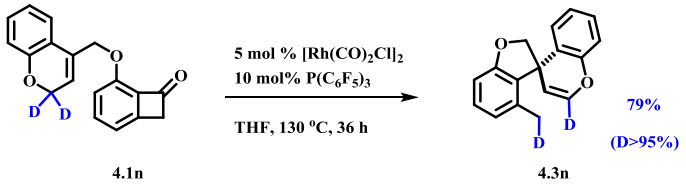
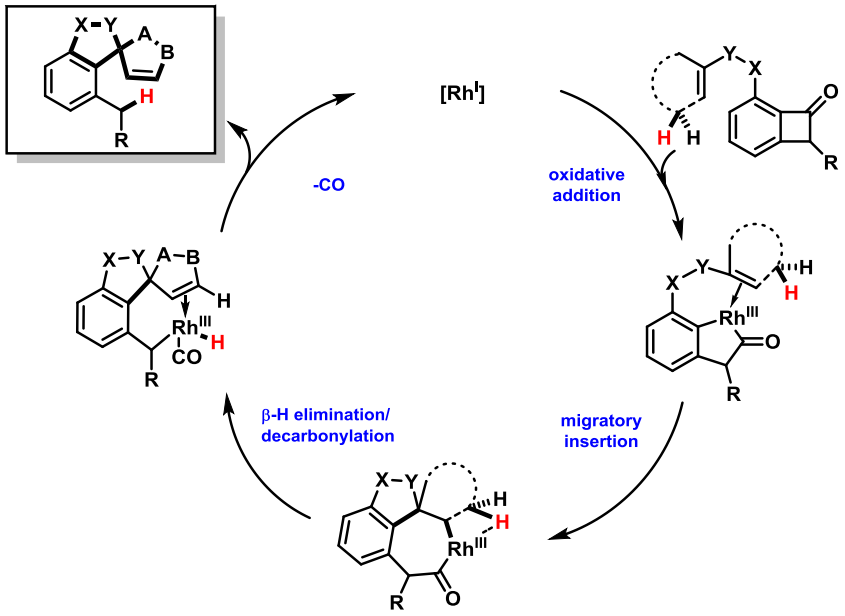


Figure 4.4 *Deuterium Labeling Experiment.*

Encouraged by the success of this deuterium study, a catalytic cycle was proposed **(Scheme 4.2)** that supports the hypothesis that this transformation undergoes β-H elimination, decarbonylation and and reductive elimination. Unlike the cut and sew transformation outlined in **Chapter 2**, this pathway delays the direct carbon carbon reductive elimination to allow for the formation of spirocyclic compounds.



Scheme 4.2. *Proposed Catalytic Cycle.*

Studies into internal linear olefins and greater substitutions throughout compounds are currently being investigated to determine potentially novel cyclization products and expand the scope of this reaction.

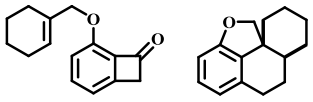
4.4 Conclusions

In conclusion, we have developed a complementary but unique method to generate all carbon-based spirocyclic compounds via a rhodium-catalyzed decarbonylative spirocyclization. In particular, this reaction operated under neutral reaction conditions, which suggests significant tolerance for both acid and base sensitive functionalization, a marked improvement on traditional spirocycle synthesis. Similarly, a broad substrate scope containing both electron-deficient and electron–rich compounds

was shown to successfully react, providing a range of structurally diverse spirocycles that suggests the potential for future application in natural product synthesis. Furthermore, to the best of our knowledge, this represents the only example of C–C activation, olefin insertion, β-H elimination and decarbonylation in a one-reaction sequence, methodology that may be investigated to unveil new tandem transformations. Further expansions of this project by extension of the substrate and reaction scope as well as the investigation into enantioselective variants are forthcoming.

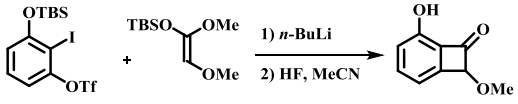
4.5 Experimental

Preparation of Benzocyclobutenone Structures for Spirocyclization



4.1a 4.2a

Compounds **4.1a** and **4.2a** are known compounds and were previously characterized by our group.[39]



S9 S10 S11

Following similar methods toward the synthesis of **2.1c**, a flame-dried, 200 mL Schlenk flask equipped with a magnetic stirring bar, a nitrogen gas balloon and a

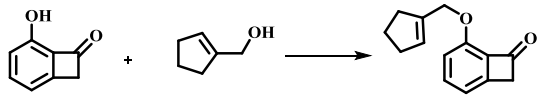
rubber septum was charged with **S9** (3.0 g, 6.2 mmol). The flask was flushed with nitrogen, THF (30 mL) and **S10**[40] (2.0 g, 9.3 mmol) were added by syringe, and the mixture was cooled to -78 °C with a dry ice-acetone bath. A solution of butyl-lithium in hexanes (2.5 M, 4.5 mL, 11.3 mmol) was added to the reaction mixture over 10 min via syringe. The reaction mixture was further stirred for 5 min at –78 °C, then water (5 mL) was added drop wise. After warming to room temperature, water (40 mL) was added, and the products were extracted with ethyl acetate (3 × 20 mL). The combined organic extract was washed with brine (40 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give crude product as dark brown oil. This was used directly for the next step without further purification.

A 250-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, a stopper and an nitrogen inlet was charged with *the* dark brown oil in CH_3CN (100 mL), and the mixture was cooled to 0 °C in an ice-water bath. Aqueous HF (27.6M, 2.2 mL, 60.7 mmol) was slowly added during 2 min via syringe. The mixture was warmed to 40°C, then stirred overnight. The reaction mixture was carefully poured into saturated aqueous sodium bicarbonate solution (60 mL), and the products were extracted with ethyl acetate (3 × 30 mL). The combined organic extract was successively washed with saturated aqueous sodium bicarbonate solution (30 mL) and brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a yellow oil residue. The residue was purified by column chromatography on silica gel to give 213.3 mg (21% over two steps) of **S11** as

viscous oil. **R_f**=0.25 (EtOAc/Hexane=1/5). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.42 (dd, *J* = 8.4, 6.8 Hz, 1H), 7.02 (d, *J* = 7.2 Hz, 1H), 6.82 (d, *J* = 5.6 Hz, 1H), 6.72-6.68 (m, 1H), 4.99-4.96 (m, 2H), 3.90 (s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 189.6, 155.6, 150.1, 139.2, 132.7, 118.3, 115.6 92.1, 57.0. **IR:** *v* 2960, 1735, 1612, 1453, 1302, 1147, 1051, 853 $cm^{-1;}$ **HRMS** calc'd. for $C_9H_8O_3Na^+$ $[M+Na]^+$: 187.0366. Found: 187.0371.

General Procedure I for the Synthesis of 4.1b, 4.1c, 4.1d, 4.1e, 4.1h, 4.1i, 4.1j, 4.1l, 4.1m and 4.1n

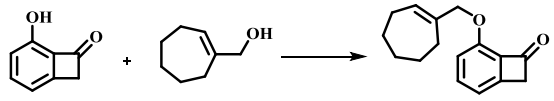
A flame-dried Schlenk flask equipped with a magnetic stirrer bar was charged with 6-hydroxybenzocyclobutanone (1.0 equiv.), PPh_3 (1.0 equiv.), allyl alcohol (1.0 equiv.) and the flask was degassed three times under nitrogen before THF was added via cannula. Then DIAD (1.0 equiv.) was added drop wise via syringe to the above solution and the reaction was heated to reflux. TLC was used to monitor the reaction (completion usually occurred within 3 h). When the reaction was finished, it was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel to afford the desired product.



S12 4.1b

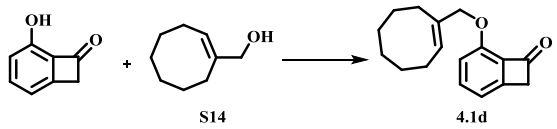
4.1b was synthesized from the known compound **S12**[41] (98 mg, 1.0 mmol) and the known 6-hydroxybenzocyclobutanone (134 mg, 1.0 mmol) following general procedure

I and was isolated as a light yellow oil (189.7 mg) in 89% yield. R_F=0.55 (EtOAc/Hexane=1/5). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.41 (dd, *J* = 8.4, 7.2 Hz, 1H), 7.00 (d, *J* = 7.2 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 5.74 (m, 1H), 4.96 (s, 2H), 3.89 (s, 2H), 2.41~2.32 (m, 4H), 1.96~1.87 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 185.0, 152.6, 150.6, 139.6, 137.7, 132.5, 28.8, 116.3, 115.0, 71.2, 51.2, 32.8, 32.5, 23.3. **IR:** *v* 1761, 1603, 1573, 1274, 1158, 1128, 1052, 782 cm^{-1}; **HRMS** calc'd. for $C_{14}H_{15}O_2^+$ $[M+H]^+$: 215.1072. Found: 215.1069.



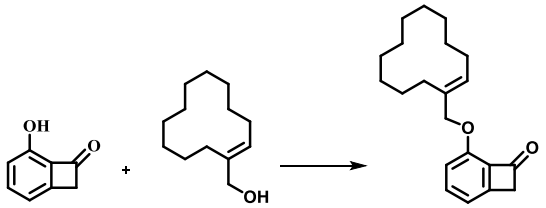
S13 4.1c

4.1c was synthesized from the known compound **S13**[42] (295 mg, 2.2 mmol) following general procedure I and was isolated as a colorless sticky oil (371.7 mg) in 71% yield. R_F=0.60 (EtOAc/Hexane=1/5). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.42 (dd, *J* = 8.4, 6.8 Hz, 1H), 7.01 (d, *J* = 6.8 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 5.96 (m, 1H), 4.76 (s, 2H), 3.90 (s, 2H), 2.24-2.20 (m, 2H), 2.18-2.01 (m, 2H), 1.79-1.71 (m, 2H), 1.58-1.46 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 185.1, 152.8, 150.6, 139.6, 137.7, 132.6, 131.1, 116.5, 115.0, 78.0, 51.2, 32.4, 30.3, 28.4, 27.0, 26.7. **IR:** *v* 1770, 1602, 1574, 1456, 1278, 1054, 781 cm^{-1}; **HRMS** calc'd. for $C_{16}H_{18}O_2Na^+$ $[M+Na]^+$: 265.1199. Found: 265.1199.



S14 4.1d

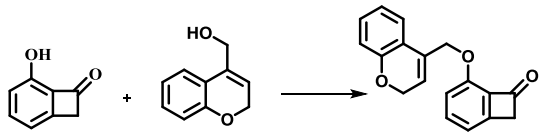
4.1d was synthesized from the known compound **S14**[43] (123.1 mg, 1.0 mmol) following general procedure I and was isolated as a colorless oil (170 mg) in 66% yield. $\mathbf{R_f}$=0.60 (EtOAc/Hexane=1/5). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.42 (dd, *J* = 8.4, 7.6 Hz, 1H), 7.00 (d, *J* = 7.6 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 5.80 (m, 1H), 4.82 (s, 2H), 3.91 (s, 2H), 2.30-2.26 (m, 2H), 2.19-2.13 (m, 2H), 1.62-1.48 (m, 8H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 185.1, 152.7, 150.6, 137.7, 136.2, 132.6, 129.4, 116.5, 114.95, 76.6, 51.2, 29.5, 28.9, 26.82, 26.40, 26.35, 26.11. **IR:** *v* 1767, 1602, 1572, 1472, 1275, 1049, 974, 782 cm^{-1}; **HRMS** calc'd. for $C_{17}H_{19}O_2^-$ $[M-H]^-$: 255.1385. Found: 255.1385.



S15 4.1e

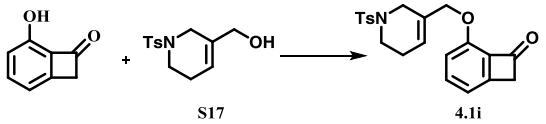
4.1e was synthesized from the known compound **S15**[44] (196.2 mg, 1.0 mmol) following the general procedure I and was isolated as a clear oil (280 mg) in 90% yield. $\mathbf{R_f}$=0.65 (EtOAc/Hexane=1/5). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.42 (dd, *J* = 8.4, 7.6 Hz, 1H), 7.02 (d, *J* = 7.6 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 5.70 (t, *J* = 8.0 Hz, 1H), 4.96 (s, 2H), 3.93 (s, 2H), 2.30-2.24 (m, 2H), 2.23-2.16 (m, 2H), 1.62-1.28 (m, 16H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 185.1, 152.9, 150.7, 137.7, 134.4, 132.89, 132.72, 116.4, 115.1, 69.6, 51.3, 34.2, 28.0, 26.90, 26.84, 25.92, 25.78, 24.47, 24.45, 23.75. **IR:** *v* 2857, 1770,

1604, 1572, 1472, 1273, 1128, 1049, 979, 782 cm^{-1}; **HRMS** calc'd. for $C_{21}H_{28}O_2^+$ $[M]^+$: 312.2089. Found: 312.2089.



S16 4.1h

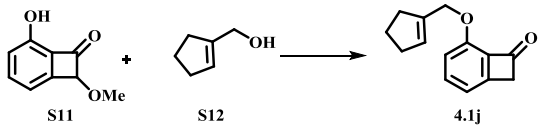
4.1h was synthesized from the known compound **S16**[45] (273 mg, 2.2 mmol) following general procedure I and was isolated as a white solid (371.7 mg) in 71% yield. R_f=0.65 (EtOAc/Hexane=1/5). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.46 (dd, *J* = 8.4, 7.2 Hz, 1H), 7.28-7.25 (m, 1H), 7.17-7.13 (m, 1H), 7.07 (d, *J* = 7.2 Hz, 1H), 6.95-6.90 (m, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 6.84-6.81 (m, 1H), 5.98 (m, 1H), 5.25 (m, 2H), 4.84 (m, 2H), 3.97 (s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 185.2, 154.2, 152.0, 150.7, 138.0, 132.6, 129.70, 129.54, 123.7, 121.53, 121.45, 120.78, 116.56, 116.13, 115.66, 71.2, 65.3, 51.4. **IR:** *v* 1760, 1603, 1574, 1273, 1222, 1129, 756 cm^{-1}; **HRMS** calc'd. for $C_{18}H_{14}O_3Na^+$ $[M+Na]^+$: 301.0835. Found: 301.0831. **Mp.** 65-67 °C



S17 4.1i

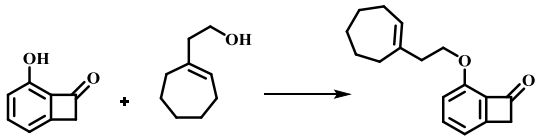
4.1i was synthesized from the known compound **S17**[46] (73.7 mg, 0.276 mmol) following general procedure I and was isolated as a white solid (102.8 mg) in 97% yield. R_f=0.25 (EtOAc/Hexane=1/3). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.67 (d, *J* = 6.8 Hz, 2H), 7.44 (dd, *J* = 8.4, 7.2 Hz, 1H), 7.30 (d, *J* = 6.8 Hz, 2H), 7.04 (d, *J* = 7.2 Hz,

1H), 6.82 (d, *J* = 8.4 Hz, 1H), 5.91 (m, 1H), 4.78 (s, 2H), 3.91 (s, 2H), 3.68 (m, 2H), 3.17 (t, *J* = 6.0 Hz, 2H), 2.43 (s, 3H), 2.25-2.23 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 185.2, 152.0, 150.6, 143.7, 138.0, 133.5, 132.4, 130.2, 129.8, 127.8, 124.9, 116.6, 115.6, 74.0, 51.3, 45.4, 42.5, 25.1, 21.7. **IR:** *v* 1760, 1603, 1475, 1339, 1271, 1095, 784, 663 cm^{-1}; **HRMS** calc'd. for $C_{21}H_{21}NO_4SNa^+$ $[M+Na]^+$: 406.1083. Found: 406.1097. **Mp**. 80-85 ºC



S11 S12 4.1j

4.1j was synthesized from **S11** and the known compound **S12** (98 mg, 1.0 mmol) following general procedure I and was isolated as a viscous oil (200.5 mg) in 83% yield. **R$_f$**=0.50 (EtOAc/Hexane=1/5). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.51 (dd, *J* = 8.4, 7.2 Hz, 1H), 7.22 (d, *J* = 7.2 Hz, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 5.77-5.72 (m, 1H), 5.50 (s, 1H), 5.05-4.92 (m, 2H), 3.53 (s, 3H), 2.44-2.30 (m, 4H), 1.97-1.87 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 186.32, 155.06, 153.56, 139.41, 138.30, 132.57, 129.06, 118.45, 115.50, 91.94, 71.41, 56.84, 32.83, 32.58, 23.39. **IR:** *v* 1772, 1604, 1574, 1472, 1273, 1128, 1049, 782 cm^{-1}; **HRMS** calc'd. for $C_{15}H_{16}O_3Na^+$ $[M+Na]^+$: 267.0992. Found: 267.1000.

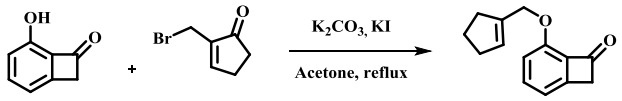


S18 4.1l

4.1l was synthesized from the known compound **S18**[47] (126.2 mg, 1.0 mmol) following the general procedure-I and was isolated as a colorless oil (225 mg) in 94% yield. R_f=0.75 (EtOAc/Hexane=1/5). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.40 (dd, *J* = 8.4, 7.2 Hz, 1H), 6.99 (d, *J* = 7.2 Hz, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 5.67 (t, *J* = 6.4 Hz, 1H), 4.42 (t, *J* = 6.4 Hz, 2H), 3.89 (s, 2H), 2.46-2.42 (m, 2H), 2.20-2.16 (m, 2H), 2.11-2.06 (m, 2H), 1.76-1.69 (m, 2H), 1.52-1.43 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 185.0, 152.8, 150.6, 140.6, 137.7, 132.5, 128.7, 116.3, 114.9, 71.4, 51.2, 39.8, 32.96, 32.70, 28.5, 27.3, 26.7. **IR:** *v* 1770, 1603, 1572, 1475, 1275, 1052, 782 cm^{-1}; **HRMS** calc'd. for $C_{17}H_{20}O_2^+$ $[M]^+$: 256.1463. Found: 256.1460.

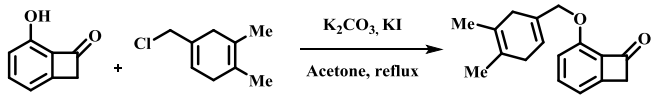
General Procedure II for the Synthesis of 4.1f, 4.1g, and 4.1k

Allyl halide (1.25 equiv.) was added in one portion to a solution of acetone containing 6-hydroxybenzocyclobutanone (1 equiv.), K_2CO_3 (5 equiv.) and KI (2 equiv.). The reaction mixture was heated to reflux and stirred overnight. Then the reaction was quenched with aqueous ammonium chloride. The aqueous phase was extracted with ethyl acetate and the combined organic extract was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue that was purified by column chromatography on silica gel.



S20 4.1f

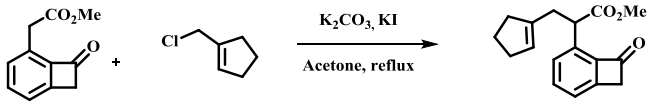
4.1f was synthesized from the known compound **S20**[48] (350 mg, 2 mmol) following general procedure II and was isolated as a white solid (180 mg) in 39% yield. R_f=0.20 (EtOAc/Hexane=1/3). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.66 (m, 1H), 7.42 (dd, *J* = 8.4, 7.2 Hz, 1H), 7.04 (d, *J* = 7.2 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 5.07 (m, 2H), 3.91 (s, 2H), 2.67-2.62 (m, 2H), 2.50-2.40 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 207.9, 184.8, 161.3, 152.0, 150.7, 141.6, 137.9, 132.5, 116.2, 115.6, 65.7, 51.4, 34.9, 27.1. **IR:** *v* 1760, 1699, 1601, 1574, 1472, 1274, 784 cm^{-1}; **HRMS** calc'd. for $C_{14}H_{12}O_3Na^+$ $[M+Na]^+$: 251.0679. Found: 251.0677. **Mp.** 68-70 °C



S21 4.1g

4.1g was synthesized from the known compound **S21**[49] (156.7 mg, 1 mmol) following general procedure II and was isolated as a colorless oil (124.2 mg) in 61% yield. R_f=0.65 (EtOAc/Hexane=1/3). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.42 (dd, *J* = 8.0, 7.2 Hz, 1H), 7.01 (d, *J* = 7.2 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 5.83 (m, 1H), 4.82 (s, 2H), 3.91 (s, 2H), 2.70-2.60 (m, 4H), 1.67 (s, 3H), 1.64 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 185.2, 152.7, 150.7, 137.8, 132.6, 131.1, 124.0, 122.85, 122.78, 116.5, 115.1,

76.0, 51.3, 33.61, 33.58, 18.64, 18.38. **IR:** *v* 1760, 1699, 1601, 1574, 1472, 1274, 784 cm^{-1}. **HRMS** calc'd. for $C_{17}H_{18}O_2Na^+$ $[M+Na]^+$: 277.1199. Found: 277.1202.



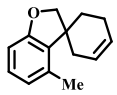
S22 **S23** **4.1k**

4.1k was synthesized from **S22** (43.8 mg, 0.23 mmol) and the known compound **S23**[50] (47 mg, 0.40 mmol) following general procedure II and was isolated as a colorless oil (50 mg) in 81% yield. R_f=0.40 (EtOAc/Hexane=1/5). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.45-7.39 (m, 2H), 7.32 (m, 1H), 5.30 (s, 1H), 4.03 (t, *J* = 8.0 Hz, 1H), 3.96 (s, 2H), 3.66 (s, 3H), 2.99-2.92 (m, 1H), 2.77-2.70 (m, 1H), 2.22-2.18 (m, 4H), 1.82-1.73 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 187.8, 173.2, 151.4, 146.5, 141.1, 135.4, 134.8, 128.1, 126.2, 122.5, 52.4, 52.2, 47.5, 35.1, 34.1, 32.6, 23.5. **IR:** *v* 1602, 1425, 1332, 1261, 1025, 783 cm^{-1}; **HRMS** calc'd. for $C_{17}H_{19}O_3^+$ $[M+H]^+$: 271.1329. Found: 271.1334.

General Procedure for the Rh-catalyzed Decarbonylative Spirocyclization (Reaction was performed at 0.2 mmol scale and 0.1 M concentration):

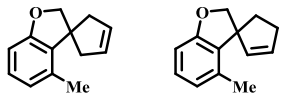
In a nitrogen filled glove box, a 1 dram vial was charged with 5 mol % $[Rh(CO)_2Cl]_2$ and 10 mol % $P(C_6F_5)_3$. A solution of the starting material in THF (2 mL) was added and the 1 dram vial was capped and the solution was maintained at 130 °C

for 36 h. The reaction was removed from the glove box, concentrated and purified by flash chromatography.



4.3a

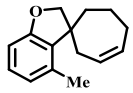
4.3a was isolated as a colorless crystal (33.6 mg) in 72% yield. R_f=0.75 (EtOAc/Hexane=1/5). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.04 (dd, *J* = 7.6, 7.6 Hz, 1H), 6.66 (d, *J* = 7.2 Hz, 1H), 6.65 (d, *J* = 7.2 Hz, 1H), 5.83-5.76 (m, 1H), 5.73-5.66 (m, 1H), 4.33 (d, *J* = 8.4 Hz, 1H), 4.22 (d, *J* = 8.4 Hz, 1H), 2.60-2.50 (m, 1H), 2.40-2.30 (m, 4H), 2.25-2.05 (m, 3H), 1.80-1.70 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 160.07, 134.83, 132.07, 128.27, 127.36, 125.33, 123.46, 107.78, 81.31, 45.75, 34.27, 29.97, 22.78, 18.62. **IR:** *v* 1590, 1461, 1232, 1021, 996, 783 cm^{-1}; **HRMS** calc'd. for $C_{14}H_{16}O^+$ $[M]^+$: 200.1201. Found: 200.1201. **Mp.** 35-40 °C.



4.3b + 4.3b'

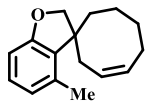
4.3b and **4.3b'** were obtained as an inseparable mixture (33.5 mg) in a combined 78% yield. **R$_f$**=0.75 (EtOAc/Hexane=1/5). **4.3b ^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.05 (dd, *J* = 8.0, 7.6 Hz, 1H), 6.71-6.64 (m, 2H), 5.80-5.74 (m, 2H), 4.42 (s, 2H), 3.03-2.94 (m, 2H), 2.64-2.57 (m, 2H), 2.26 (s, 3H). **4.3b' ^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.05 (dd, *J* = 8.0, 7.6 Hz, 1H), 6.71-6.64 (m, 2H), 5.91 (dt, *J* = 5.6, 2.47 Hz, 1H), 5.70 (dt, *J* = 5.6,

2.4 Hz, 1H), 4.32 (d, *J* = 8.4 Hz, 1H), 4.23 (d, *J* = 8.8 Hz, 1H), 2.57-2.52 (m, 2H), 2.24 (s, 3H), 2.22-2.15 (m, 2H). **4.3b & 4.3b' ^{13}C NMR** (101 MHz, $CDCl_3$): δ 159.99, 159.82, 135.50, 134.795, 134.14, 132.54, 132.28, 129.34, 128.38, 128.12, 123.33, 123.16, 107.37, 107.32, 88.08, 81.87, 59.34, 51.04, 46.75, 36.58, 32.10, 18.19, 17.43. **IR:** *v* 2001, 1591, 1518, 1483, 1248, 1092, 985, 776 cm^{-1}; **HRMS** calc'd. for $C_{13}H_{14}O^+$ $[M]^+$: 186.1045. Found: 186.1047.



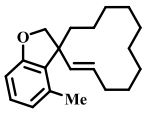
4.3c

4.3c was isolated as a colorless oil (41.4 mg) in 86% yield. R_f=0.70 (EtOAc/Hexane=1/5). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.01 (dd, *J* = 7.6, 7.6 Hz, 1H), 6.63 (d, *J* = 7.6 Hz, 2H), 6.65 (d, *J* = 7.2 Hz, 1H), 5.96 (m, 1H), 5.77 (m, 1H), 4.34-4.24 (m, 2H), 3.01-2.93 (m, 1H), 2.41 (s, 3H), 3.60-2.15 (m, 4H), 2.08-2.01 (m, 1H), 1.79 (m, 1H), 1.47 (m,1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 159.23, 134.46, 134.42, 134.14, 128.21, 128.02, 123.44, 107.81, 79.12, 48.64, 39.78, 36.20, 28.90, 23.54, 19.09. **IR:** *v* 1588, 1461, 1247, 1028, 988, 774, 737 cm^{-1}; **HRMS** calc'd. for $C_{15}H_{18}O^+$ $[M]^+$: 214.1358. Found: 214.1358.



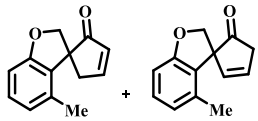
4.3d

4.3d was isolated as a colorless oil (25.6 mg) in 56% yield. $\mathbf{R_f}$=0.75 (EtOAc/Hexane=1/5). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.01 (dd, *J* = 7.6, 7.6 Hz, 1H), 6.66-6.61 (m, 2H), 5.84-5.69 (m, 2H), 4.40-4.24 (m, 2H), 2.92-2.84 (m, 1H), 2.42 (s, 3H), 2.30-2.22 (m, 1H), 2.16-2.05 (m, 2H), 1.92-1.83 (m, 1H), 1.70-1.58 (m, 4H), 1.44-1.38 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 159.3, 134.43, 134.32, 132.6, 127.95, 127.76, 123.5, 107.9, 80.3, 52.1, 35.2, 34.7, 28.4, 24.7, 21.2, 19.5. **IR:** *v* 1587, 1466, 1245, 1231, 988, 773, 732 cm^{-1}; **HRMS** calc'd. for $C_{16}H_{20}O^+$ $[M]^+$: 228.1514. Found: 228.1517.



4.3e

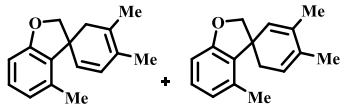
4.3e was isolated as a colorless oil (51.2 mg) in 90% yield. $\mathbf{R_f}$=0.80 (EtOAc/Hexane=1/5). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.02 (dd, *J* = 8.0, 8.0 Hz, 1H), 6.68-6.62 (m, 2H), 5.82 (d, *J* = 16.0 Hz, 1H), 5.51-5.43 (m, 1H), 4.58 (d, *J* = 8.8 Hz, 1H), 4.24 (d, *J* = 8.8 Hz, 1H), 2.42 (s, 3H), 2.29-2.20 (m, 1H), 2.06-1.81 (m, 3H), 1.66-1.22 (m, 14H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 159.3, 134.5, 132.09, 132.00, 129.2, 128.1, 123.5, 107.9, 78.5, 53.1, 35.9, 31.8, 26.8, 25.74, 25.04, 24.48, 24.33, 24.25, 21.91, 19.3. **IR:** *v* 1588, 1463, 1250, 1077, 993, 773, 738 cm^{-1}; **HRMS** calc'd. for $C_{20}H_{28}O^+$ $[M]^+$: 284.2140. Found: 284.2139.



4.3f 4.3f' = 1.4 : 1

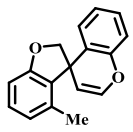
4.3f was isolated as a colorless oil (11.2 mg) in 29% yield. R_f=0.30 (EtOAc/Hexane=1/5). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.84 (dt, *J* = 5.6, 2.8 Hz, 1H), 7.08 (dd, *J* = 8.0, 7.6 Hz, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 6.65 (d, *J* = 7.6 Hz, 1H), 6.04 (dt, *J* = 5.6, 2.4 Hz, 1H), 4.57 (d, *J* = 8.8 Hz, 1H), 4.38 (d, *J* = 8.8 Hz, 1H), 3.16-3.03 (m, 2H), 2.00 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 209.79, 163.05, 160.96, 134.40, 134.02, 129.48, 128.12, 123.15, 107.77, 82.20, 57.37, 45.29, 18.31. **IR:** *v* 1750, 1597, 1420, 1223, 775, 712 cm^{-1}; **HRMS** calc'd. for $C_{13}H_{12}O_2^+$ $[M]^+$: 200.0837. Found: 200.0838.

4.3f' was isolated as a colorless oil (8.0 mg) in 21% yield. R_f=0.45 (EtOAc/Hexane=1/5). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.08 (dd, *J* = 8.0, 7.6 Hz, 1H), 6.70 (d, *J* = 8.0 Hz, 1H), 6.63 (d, *J* = 7.6 Hz, 1H), 6.29 (dt, *J* = 7.2, 2.4 Hz, 1H), 6.15 (dt, *J* = 7.2, 2.4 Hz, 1H), 4.55 (d, *J* = 8.8 Hz, 1H), 4.36 (d, *J* = 8.8 Hz, 1H), 3.20-3.02 (m, 2H), 2.08 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 216.72, 160.96, 135.31, 134.23, 129.78, 128.04, 124.01, 123.01, 107.87, 78.91, 72.45, 63.78, 42.32, 25.39, 17.68, 5.397. **IR:** *v* 1749, 1587, 1470, 1251, 986, 774, 715 cm^{-1}; **HRMS** calc'd. for $C_{13}H_{13}O_2^+$ $[M+H]^+$: 201.0916. Found: 201.0916.



4.3g 4.3g' in a 2.5 : 1 ratio

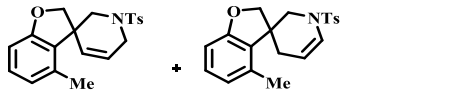
4.3g and **4.3g'** were obtained as an inseparable mixture (29.4 mg) in a combined 65% yield. **R**$_f$=0.75 (EtOAc/Hexane=1/5). **4.3g ^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.05 (dd, *J* = 8.0, 8.0 Hz, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 6.65 (d, *J* = 8.0 Hz, 1H), 5.89 (d, *J* = 9.2 Hz, 1H), 5.66 (d, *J* = 9.2 Hz, 1H), 4.48 (d, *J* = 8.8 Hz, 1H), 3.96 (d, *J* = 8.8 Hz, 1H), 2.65-2.57 (m, 1H), 2.27-2.20 (m, 1H), 2.34 (s, 3H), 1.76 (s, 3H), 1.73 (s, 3H). **4.3g' ^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.03 (dd, *J* = 8.0, 8.0 Hz, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 6.64 (d, *J* = 8.0 Hz, 1H), 5.55 (m, 1H), 5.50 (brs, 1H), 4.57 (d, *J* = 8.8 Hz, 1H), 3.92 (d, *J* = 8.8 Hz, 1H), 2.57-2.50 (m, 1H), 2.36 (s, 3H), 2.35-2.27 (m, 1H), 1.85 (s, 3H), 1.82 (s, 3H). **4.3g & 4.3g' ^{13}C NMR** (101 MHz, $CDCl_3$): δ 159.7, 135.39, 135.32, 134.4, 133.34, 132.99, 132.75, 130.5, 128.44, 128.32, 127.02, 126.31, 125.91, 123.68, 123.32, 123.26, 120.5, 107.4, 79.71, 79.21, 47.28, 46.96, 40.2, 33.7, 20.05, 19.64, 19.48, 19.32, 19.15, 17.4. **IR:** *v* 1591, 1470, 1468, 1247, 1215, 981, 774, 745 cm^{-1}; **HRMS** calc'd. for $C_{16}H_{18}O^+$ $[M]^+$: 226.1358. Found: 226.1356.



4.3h

4.3h was isolated as a colorless oil (35.5 mg) in 71% yield. R$_f$=0.85 (EtOAc/Hexane=1/5). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.20-7.14 (m, 1H), 7.11 (dd, *J* = 8.0, 7.6 Hz, 1H), 7.02-6.97 (m, 2H), 6.96-6.92 (m, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 6.67

(d, *J* = 6.0 Hz, 1H), 6.64 (m, 1H), 4.98 (d, *J* = 7.2 Hz, 1H), 4.64 (d, *J* = 8.8 Hz, 1H), 4.47 (d, *J* = 8.8 Hz, 1H), 2.01 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 159.1, 149.8, 139.7, 136.4, 132.0, 129.31, 128.56, 128.24, 125.0, 124.4, 123.6, 116.2, 107.6, 105.3, 87.7, 45.5, 17.4. **IR:** *v* 2004, 1665, 1485, 1452, 1247, 1051, 983, 757 cm^{-1}; **HRMS** calc'd. for $C_{17}H_{15}O_2^+$ $[M+H]^+$: 251.1072. Found: 251.1071.



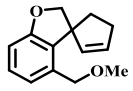
4.3i **4.3i'** **in a 3.2 : 1 ratio**

4.3i was isolated as a colorless oil (36.3 mg) in 53% yield. R_f=0.30 (EtOAc/Hexane=1/5). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.64 (m, 2H), 7.31 (m, 2H), 7.09 (dd, *J* = 8.0, 7.6 Hz, 1H), 6.69 (d, *J* = 7.6 Hz, 1H), 6.62 (d, *J* = 8.0 Hz, 1H), 5.90 (m, 2H), 4.70 (d, *J* = 9.2 Hz, 1H), 4.16-4.05 (m, 2H), 3.80-3.74 (m, 1H), 3.21-3.15 (m, 1H), 2.52-2.47 (m, 1H), 2.43 (s, 3H), 2.13 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 160.9, 144.0, 135.5, 133.3, 129.95, 129.60, 129.46, 127.75, 127.45, 124.6, 123.0, 108.1, 78.7, 49.2, 48.7, 44.6, 21.7, 17.8. **IR:** *v* 1645, 1589, 1486, 1346, 1165, 1092, 776, 665 cm^{-1}; **HRMS** calc'd. for $C_{20}H_{21}NO_3SNa^+$ $[M+Na]^+$: 378.11340. Found: 378.11470.

4.3i' was isolated as a colorless oil (11.3 mg) in 16% yield. R_f=0.35 (EtOAc/Hexane=1/5). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.68 (m, 2H), 7.34 (m, 2H), 7.06 (dd, *J* = 8.0, 7.6 Hz, 1H), 6.79 (m, 1H), 6.67-6.61 (m, 2H), 4.94 (m, 1H), 4.12-4.02 (m, 2H), 3.80-3.75 (m, 1H), 3.39-3.34 (m, 1H), 2.62-2.55 (m, 1H), 2.45 (s, 3H), 2.21 (s, 3H), 2.09-2.01 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 160.6, 144.2, 135.21, 134.73,

130.1, 129.4, 127.8, 127.1, 125.4, 123.6, 108.2, 104.4, 80.9, 49.2, 45.3, 31.2, 21.8, 18.4. **IR:** *v* 1519, 1484, 1392, 1266, 1092, 1052, 984, 741 cm^{-1}; **HRMS** calc'd. for $C_{20}H_{21}NO_3SNa^+$ $[M+Na]^+$: 378.1134. Found: 378.1147.

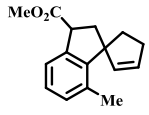
The direct reductive elimination product **2i** was isolated as a white solid (10.0 mg) in 14% yield. $\mathbf{R_f}$=0.25 (EtOAc/Hexane=1/3). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.54 (m, 2H), 7.27 (m, 2H), 7.18 (dd, *J* = 8.0, 7.6 Hz, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 6.67 (d, *J* = 7.6 Hz, 1H), 5.09 (d, *J* = 8.8 Hz, 1H), 4.27 (dd, *J* = 8.8, 2.4 Hz, 1H), 3.85-3.80 (m, 1H), 3.77-3.71 (m, 1H), 3.55-3.40 (m, 2H), 2.57-2.51 (m, 2H), 2.41 (s, 3H), 2.45-2.17 (m, 1H), 1.92 (dd, *J* = 11.6, 2.4 Hz, 1H), 1.76-1.66 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 1-208.5, 159.3, 144.0, 133.0, 130.78, 130.76, 130.0, 127.6, 127.2, 119.4, 108.7, 81.8, 50.44, 50.31, 45.6, 43.1, 40.8, 22.5, 21.7. **IR:** *v* 1706, 1645, 1471, 1338, 1164, 1105, 961, 756 cm^{-1}; **HRMS** calc'd. for $C_{21}H_{21}NO_4SNa^+$ $[M+Na]^+$: 406.1083. Found: 406.1097.



4.3j

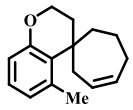
4.3j was isolated as a colorless oil (25.5 mg) in 59% yield. $\mathbf{R_f}$=0.55 (EtOAc/Hexane=1/5). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.15 (dd, *J* = 8.0, 7.6 Hz, 1H), 6.93 (d, *J* = 8.0 Hz, 1H), 6.75 (d, *J* = 7.6 Hz, 1H), 5.93 (m, 1H), 5.73 (m, 1H), 4.50-4.15 (m, 4H), 3.37 (s, H), 2.53 (m, 2H), 2.25-2.19 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 160.2, 135.5, 134.1, 132.8, 131.5, 128.7, 121.4, 109.3, 81.8, 70.4, 59.4, 58.3,

37.8, 32.0. **IR:** *v* 1590, 1519, 1480, 1248, 1092, 986, 773 cm^{-1}; **HRMS** calc'd. for $C_{14}H_{16}O_2^+$ $[M]^+$: 216.1150. Found: 216.1151.



4.3k

4.3k was isolated after subsequent hydrogenation (with 10% Pd/C under 1atm H_2) as colorless oil (27.8 mg) in 57% yield (over two steps). R_f=0.35 (EtOAc/Hexane=1/5). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.16 (d, *J* = 7.6 Hz, 1H), 7.10 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.02 (m, 1H), 3.99 (t, *J* = 8.0 Hz, 1H), 3.75 (s, 3H), 2.37 (s, 3H), 2.31-2.24 (m, 3H), 1.92-1.64 (m, 8H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 174.9, 147.6, 140.8, 133.9, 130.9, 126.8, 122.5, 55.3, 52.2, 48.2, 45.8, 38.61, 38.3, 26.1, 19.2. **IR:** *v* 1740, 1504, 1466, 1168, 971, 765 cm^{-1}; **HRMS** calc'd. for $C_{16}H_{20}O_2Na^+$ $[M+Na]^+$: 267.1356. Found: 267.1356.



4.3l

4.3l was isolated as a colorless oil (36.1 mg) in 79% yield. R_f=0.80 (EtOAc/Hexane=1/5). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.98 (dd, *J* = 8.0, 7.6 Hz, 1H), 6.73-6.66 (m, 2H), 5.92-5.84 (m, 1H), 5.69-5.62 (m, 1H), 4.15-4.02 (m, 2H), 3.45-3.36 (m, 1H), 2.59 (s, 3H), 2.52-2.42 (m, 1H), 2.38-1.58 (m, 8H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 154.7, 137.6, 132.5, 131.3, 128.4, 126.8, 125.3, 115.9, 62.1, 39.98, 37.15,

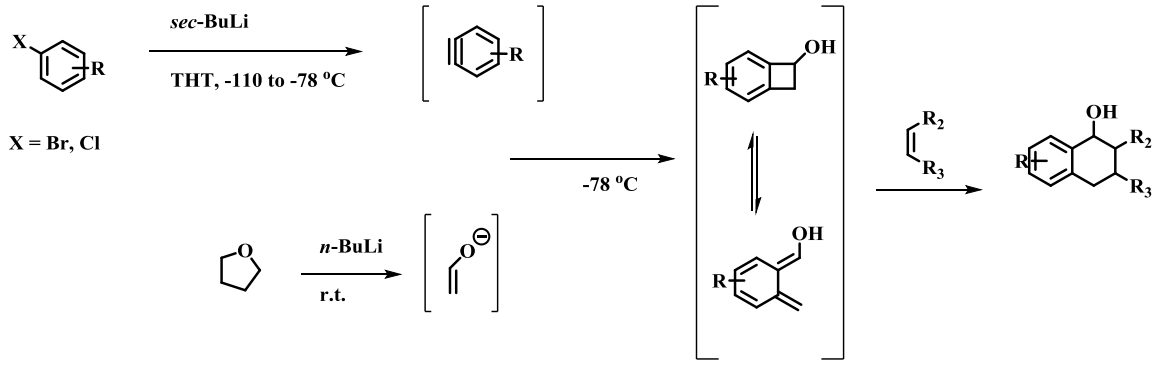
37.06, 34.1, 29.4, 23.9, 22.5. **IR:** *v* 1580, 1463, 1257, 1030, 775, 737 cm^{-1}; **HRMS** calc'd. for $C_{16}H_{20}O^{+}$ $[M]^{+}$: 228.1514. Found: 228.151.

Chapter 5: Benzocyclobutenone Derivative Synthesis

(With Mr. Penghao Chen)

5.1 Introduction

The development of novel synthetic methodologies toward accessing a library of derivatized compounds is of significant importance in the field of organic synthesis. Although previous work has outlined the use of rhodium-mediated chemistry to access a variety of fused functionalized ring systems, two equally challenging problems remain unsolved regarding this methodology. One is the reliable, large-scale production of substrate percursors capable of cyclization and the other is the early-stage functionalization to afford a diverse array of products. Recently, Wu and coworkers discovered a multicomponent one-pot coupling to afford a variety of bicyclic and tetracyclic ring systems **(Scheme 5.1)**[51]



Scheme 5.1 *One-pot Benzocyclobutenol Synthesis*

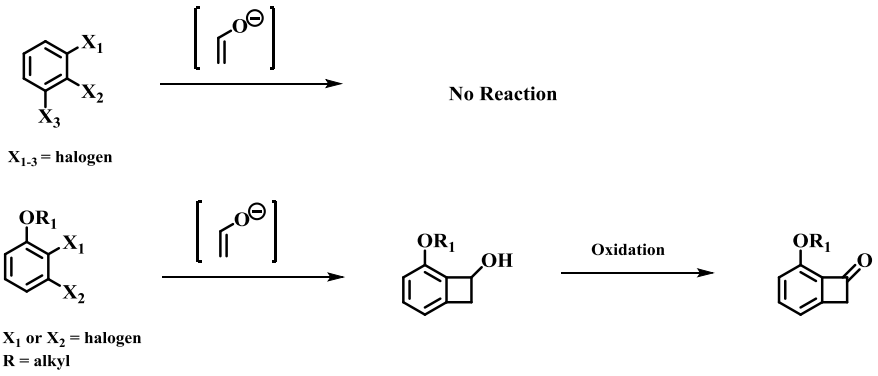
Their chemistry was found to be tolerant of a variety of substrates and by using a cyclic imine precursor, the core structure of berbine derivatives were rapidly constructed. Utilizing benzyne chemistry shares a similar structural scaffold to the desired precursors for our rhodium chemistry and was thusly investigated toward a library synthesis of substrates.

5.2 Research Objectives

In this chapter, we aim to synthesize benzocyclobutenone derivatives through a benzyne mediated key step, followed by a simple oxidation and (if necessary) deprotection. Rather than further functionalize the intermediates outlined in **Scheme 5.1** by introducing dieneophiles, we instead propose their isolation. Key to our success is the use of readily available chemical precursors and the elimination of long synthetic sequences that plagued previous efforts toward benzocyclobuenone synthesis. A variety of substrates have been examined and optimized conditions have been discovered outlining a three step sequence to functionalized products.

5.3 Results and Discussion

The early investigations into this portion of work studied the reactivity halobenzene compounds (whose syntheses are outlined in later supplemental information) in benzyne-mediated reactions. **Scheme 5.2** highlights the general scope of the transformation, utilizing a ring-opened tetrahydrofuran as the enol coupling partner for the [2+2] cyclization.



Scheme 5.2 *Benzocyclobutenone Synthesis*

Although simple halobenzenes were found incapable of affording desired products (regardless of substitution pattern and number of halogens present), it was discovered that halogen (-Cl, -Br, -I) substitution at both the *–ortho* or *–meta* positions to a phenolic oxygen underwent this transformation smoothly in moderate yields (**Table 5.1).** Although free phenol and silyl-protected alcohols did not afford any desired product, the use of benzyl as a protecting group afforded benzocyclobutanols in modest yields. Similarly, the conversion of phenol into an alkyl phenyl ether afforded products capable of cyclization whose functionalities remained intact. Poly-substitution on the phenyl backbone inhibited reactivity, except in the case of a methyl substituent in substrate **5.6a**. Further derivatization of the heteroatom linkage at this time has proven unsuccessful.

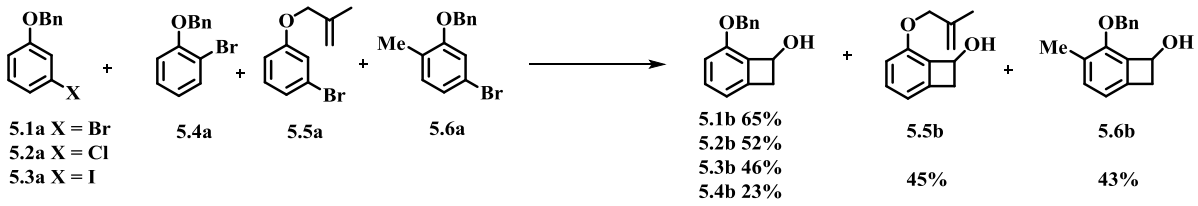


Table 5.1 *Substrate Scope for [2+2] Cyclization*

Although detailed in later supplemental information, it is important to note that these [2+2] intermediates were capable of facile oxidation to the desired "cut and sew" chemistry precursors under a variety of oxidative conditions. In situations containing benzyl-protected compounds, a unique deprotection was developed and implemented, as traditional debenzylation conditions were discovered to destroy the cyclobutanone ring.

5.4 Conclusions

The synthesis of benzocyclobutenone derivatives was achieved in synthetically fewer steps than our previous investigations. A pendant heteroatom linkage allowed for further functionalization and proved tolerant of the reaction conditions. Further experimentation (most notably, the expansion of the substrate scope) is currently in progress. Future applications to a class of natural products, as well as expansions of olefinic coupling partners and phenyl precursors are all viable expansions of this methodology.

5.5 Experimental

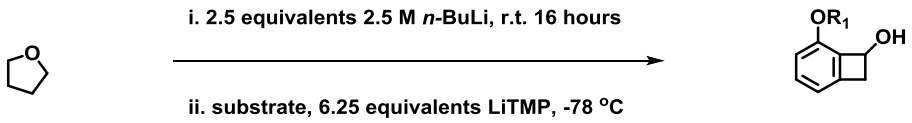
Benzyl protected phenols 5.1a-5.4a are commercially available compounds.

Synthesis of 5.5a

A flame-dried, 40 mL sealed vial equipped with a magnetic stirring bar was charged with 3-bromophenol (1.72 g, 1 mmol), K_2CO_3 (1.72 g, 1.2 mmol), 3-chloro-2-methyl-propene (1.72 g, 1.2 mmol) and a catalytic amount of KI. The vial was flushed with nitrogen, acetone (20 mL) was added by syringe, and the mixture was heated to reflux with a pi-block and allowed to stir overnight. Upon completion by TLC, the flask was cooled to room temperature water (20 mL) was added, and the products were extracted with ethyl acetate (3 × 20 mL). The combined organic extract was washed with brine (40 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give crude product as a yellow oil. This was used directly for the next step without further purification.

5.5a R_f=0.56 (EtOAc/Hexane=1/5). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.11 (m, 3H), 6.84 (dq, *J* = 4.0 Hz, 1H), 5.06 (d, *J* = 8.0 Hz, 2H), 4.39 (s, 2H), 1.81 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 160, 140, 130, 124, 123, 120, 119, 113, 72, 19

Synthesis of Benzocyclobutanols



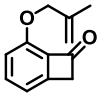
A flame-dried, 50 mL Schlenk flask equipped with a magnetic stirring bar, a nitrogen gas balloon and a rubber septum was charged with THF (12 mL) and cooled to 0 °C with an ice bath. A solution of butyl-lithium in hexanes (2.5 M, 1 mL, 2.5 mmol) was added to the reaction mixture over 10 min via syringe. The reaction mixture was further stirred for 16 hours at room temperature.

A flame-dried, 25 mL Schlenk flask equipped with a magnetic stirring bar, a nitrogen gas balloon and a rubber septum was charged with THF (5 mL) and TMP (1.06 mL, 6.25 mmol) and cooled to 0 °C with an ice bath. A solution of butyl-lithium in hexanes (2.5 M, 2.5 mL, 6.25 mmol) was added to the reaction mixture over 10 min via syringe. The reaction mixture was further stirred for 30 minutes.

The 50 mL Schlenk flask was further cooled to -78 °C using a dry ice-acetone bath. To this flask was added the LiTMP solution (outlined above) and 1.0 mmol of the desired substrate. This flask was allowed to stir cold and monitored by TLC to full consumption of the starting material (5 minutes to 4 hours). After warming to room temperature, water (40 mL) was added, and the products were extracted with ethyl acetate (3 × 20 mL). The combined organic extract was washed with brine (40 mL),

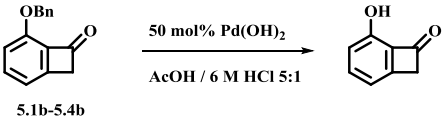
dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give crude product as dark brown oil. This was used directly for the next step without further purification.

A 100-mL round-bottomed flask equipped with a magnetic stirring bar, a stopper and a nitrogen inlet was charged with *the* dark brown oil in CH_2Cl_2 (60 mL), and the mixture was cooled to 0 °C in an ice-water bath. Pyridinium chlorochromate (0.230 g, 1.1 mmol) was slowly added during 2 min via spatula. The mixture was then stirred at room temperature and monitored by TLC until completion. The reaction mixture was carefully filtered through a pad of Celite and the combined organic extracts were successively concentrated. The residue was purified by column chromatography on silica gel to give 94 mg (42% over two steps) of the desired product **5.5b** as a yellow oil.



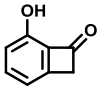
Compound **5.5b** has been previously fully characterized.[14]

Benzyl Deprotection of Benzocyclobutenones

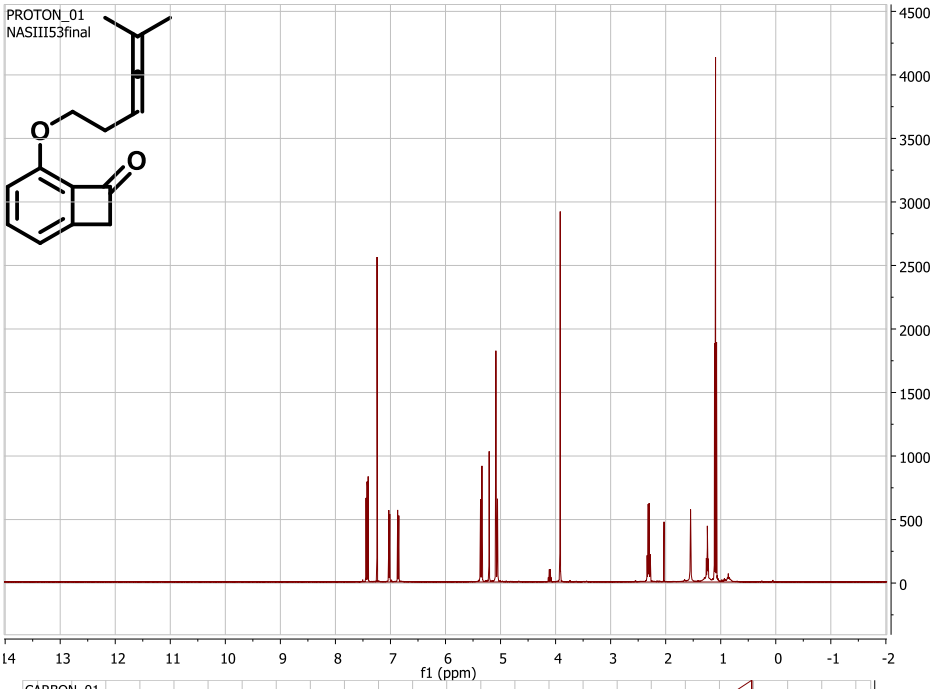


5.1b-5.4b

A flame-dried, 50 mL Schlenk flask equipped with a magnetic stirring bar, a hydrogen gas balloon and a rubber septum was charged with a 5:1 *v/v* solution of glacial acetic acid (10 mL) and 6 M HCl (2 mL) and substrate **5.1b**. $Pd(OH)_2$ (50 mol%) was added to the reaction mixture in one portion and the reaction mixture was further stirred for 4 hours at room temperature until completion by TLC. The mixture was opened to the air, filtered through a pad of Celite and concentrated under reduced pressure to give crude product as dark brown oil. The residue was purified by column chromatography on silica gel to give 85% of the desired product as a tan solid.



This compound has been previously fully characterized.[14]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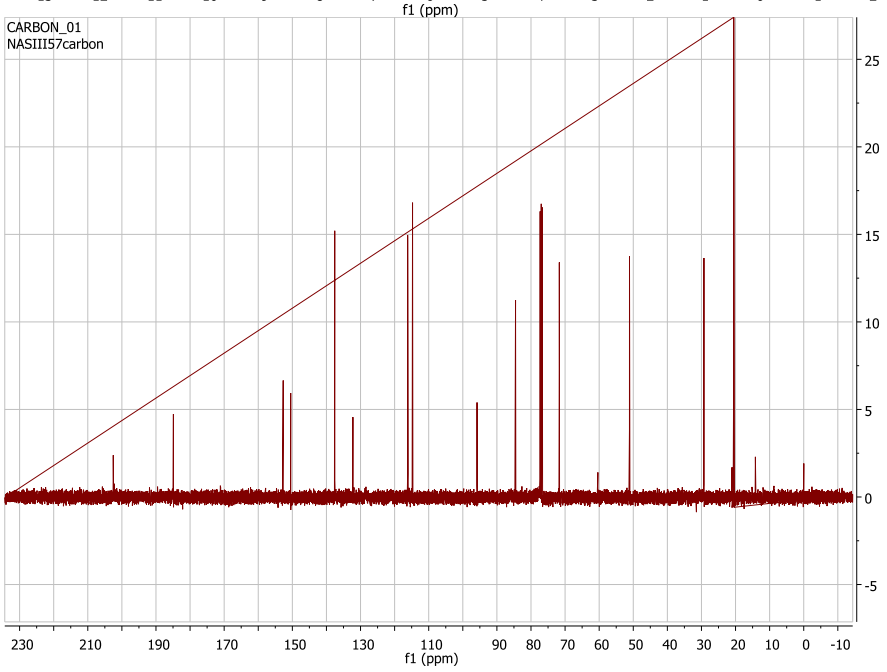
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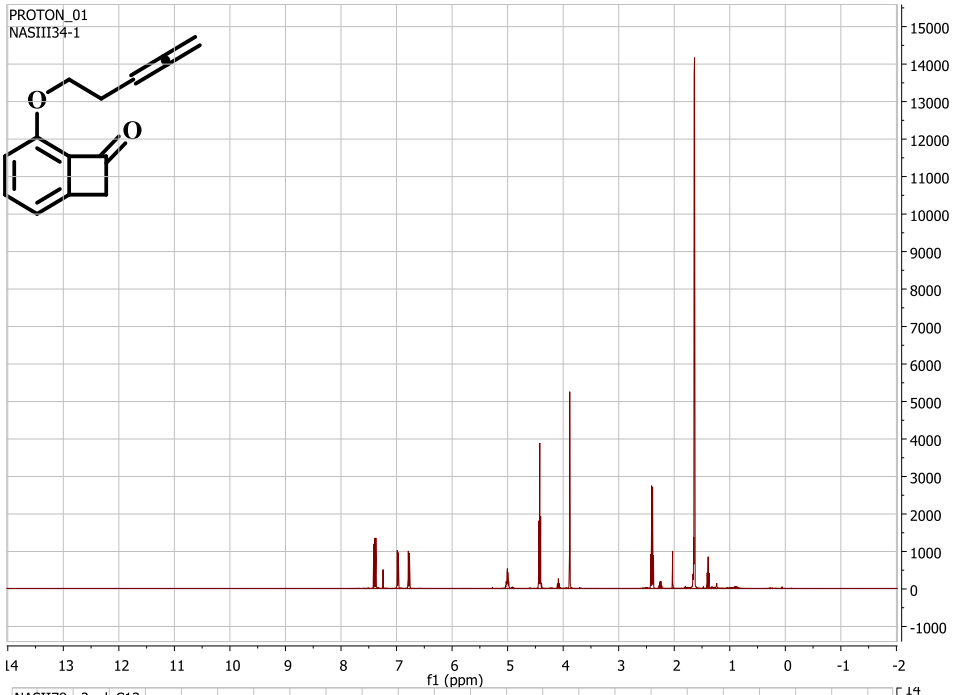
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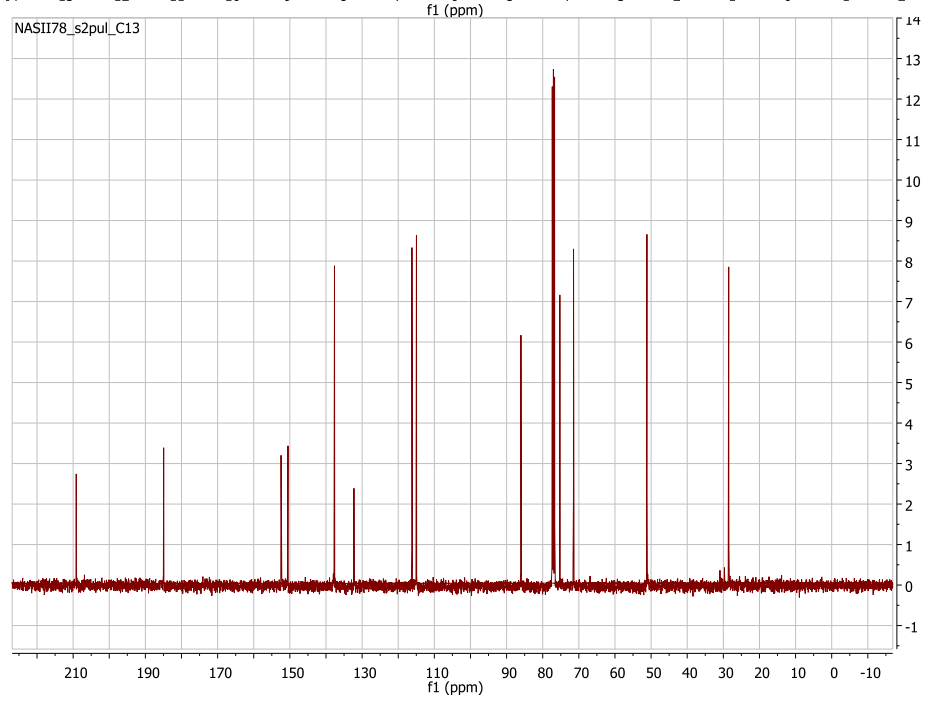
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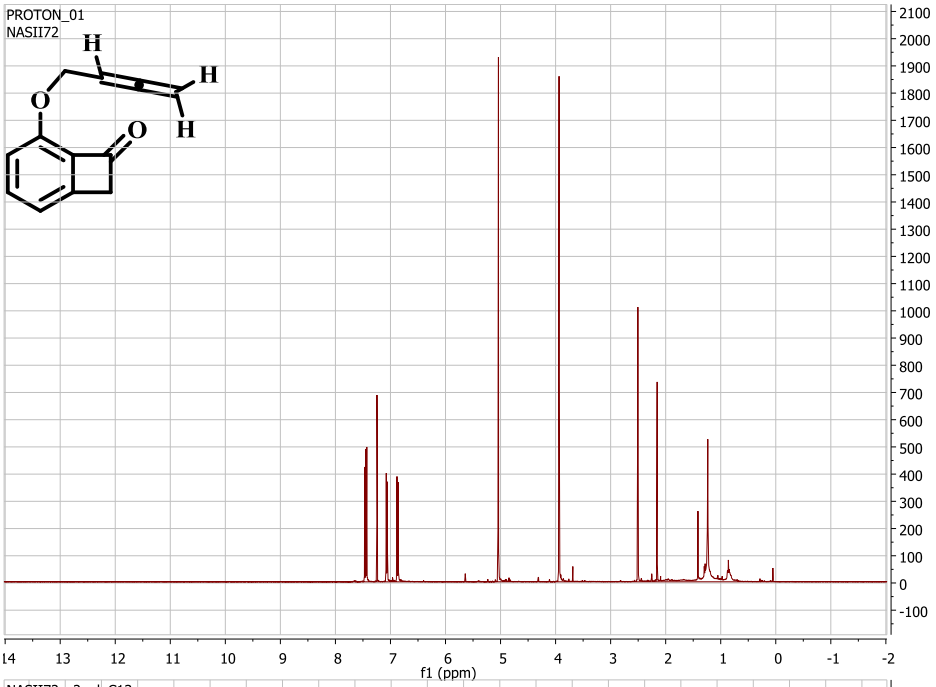
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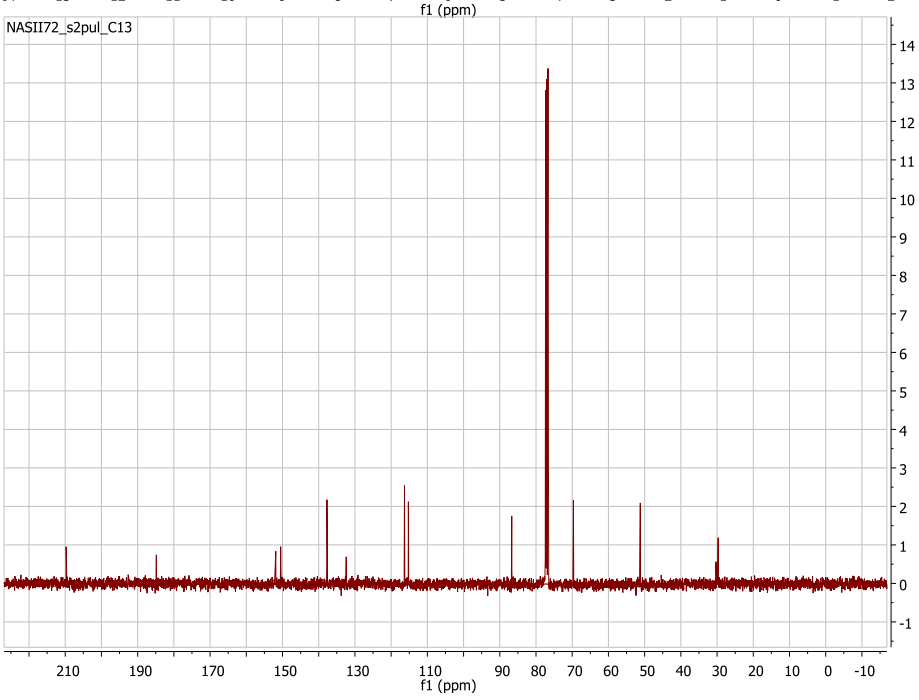
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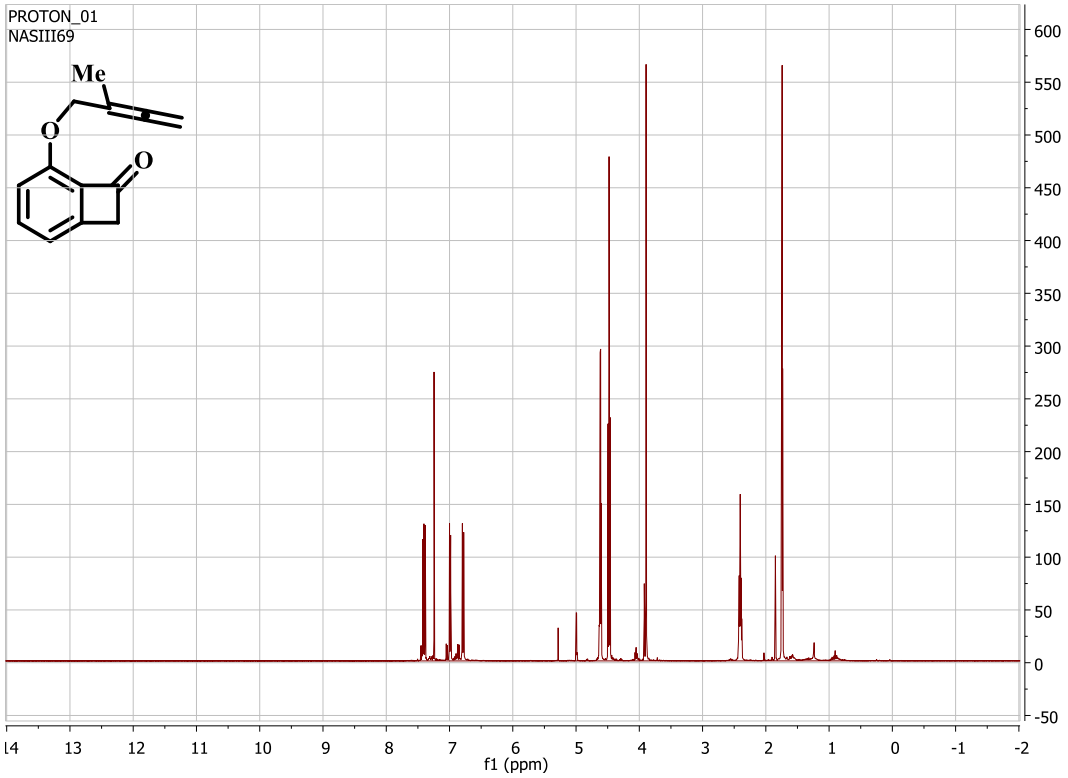
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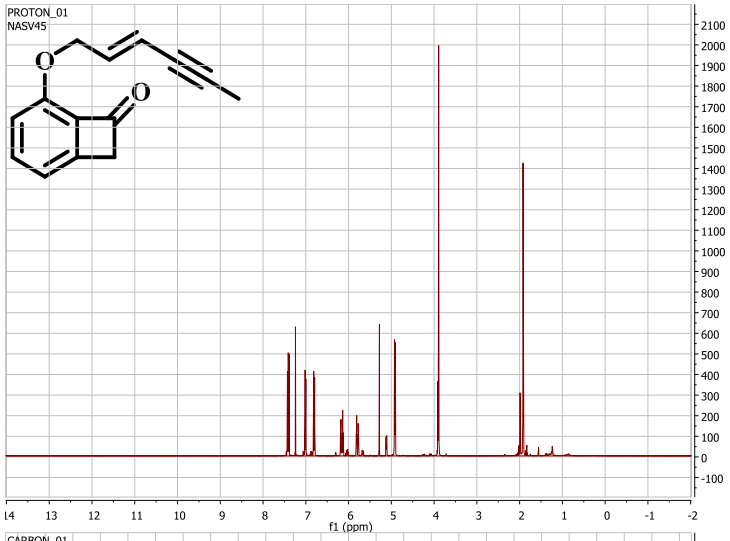
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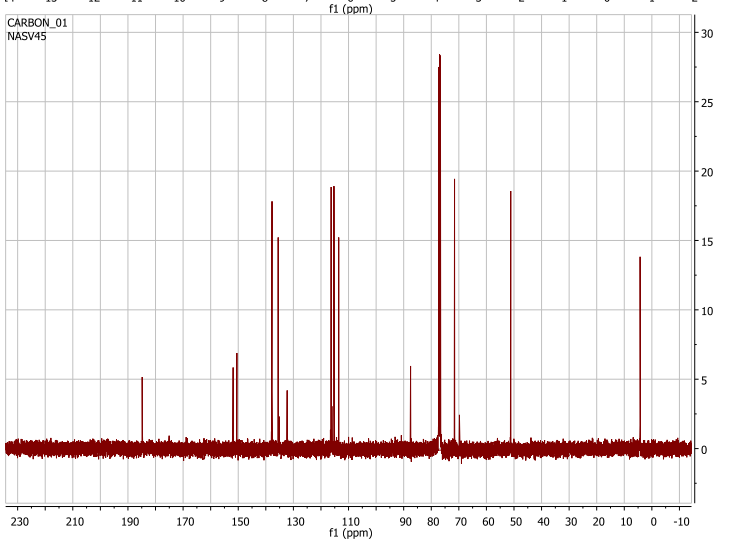
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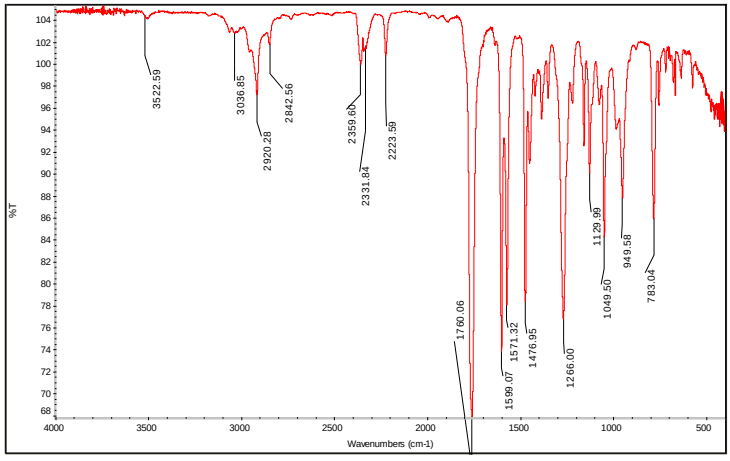
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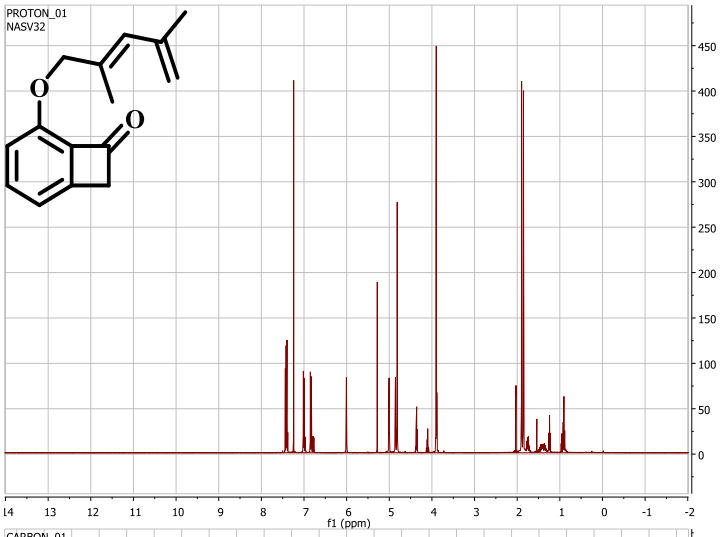
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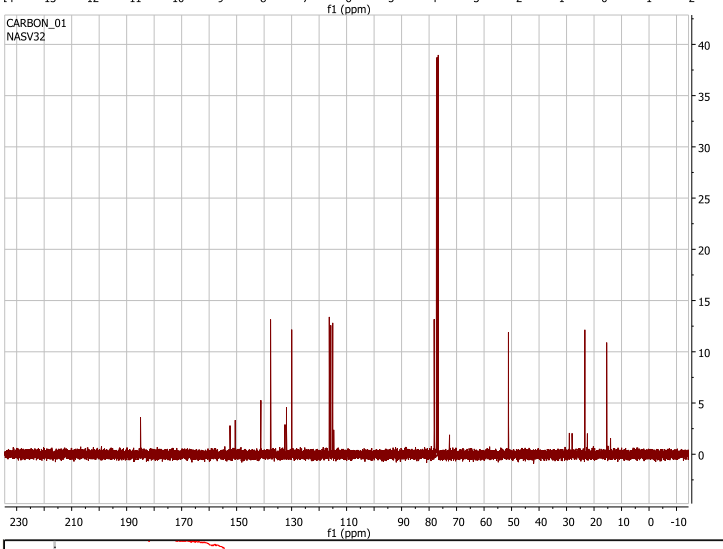
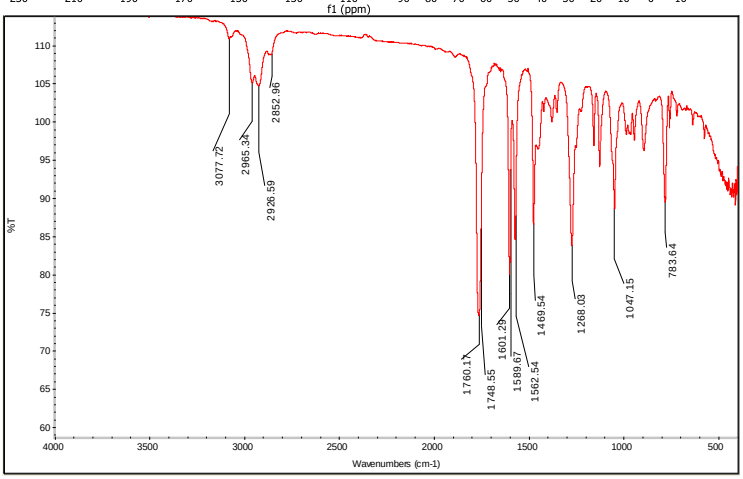
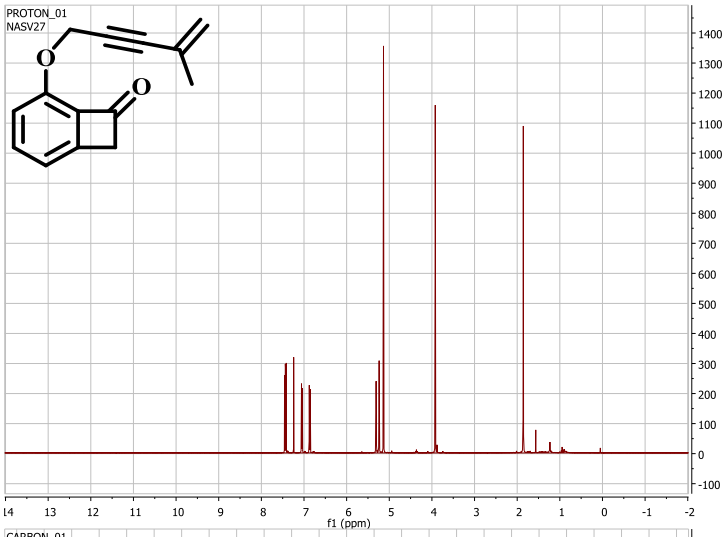
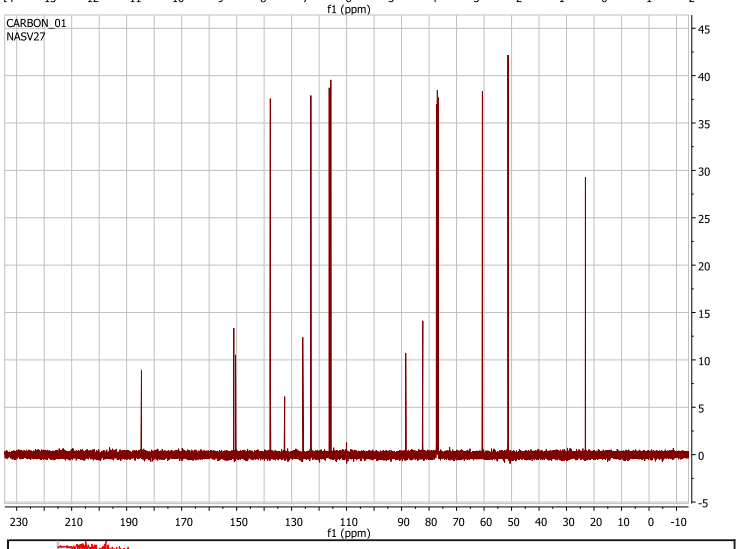
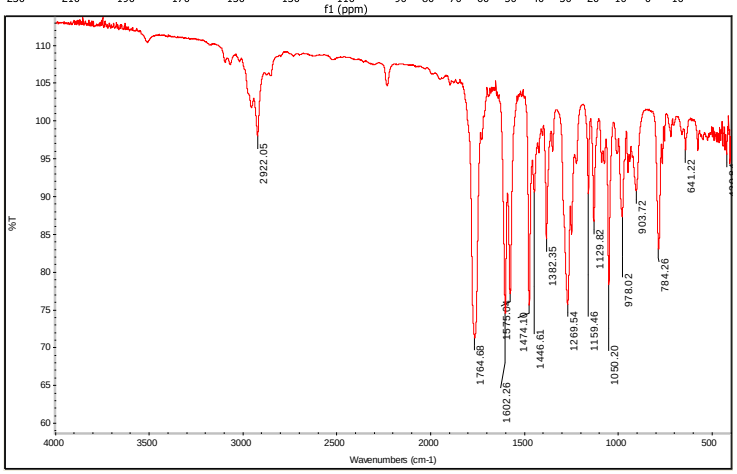
O
f1 (ppm)

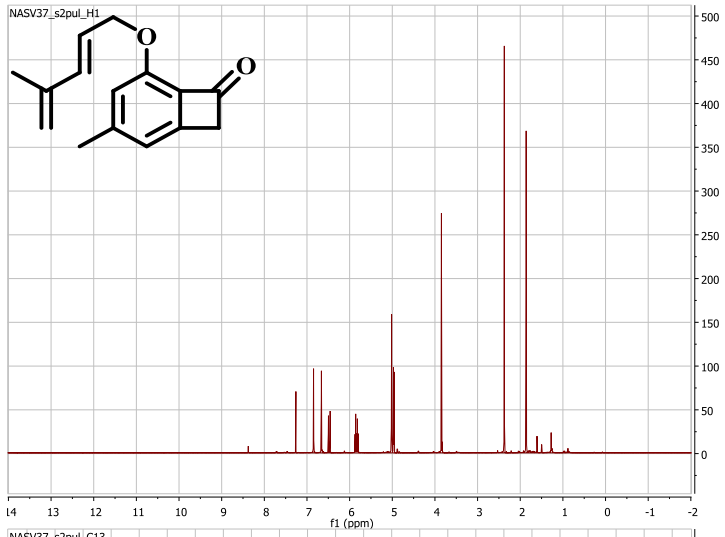

CARBON_01
NASV32
f1 (ppm)

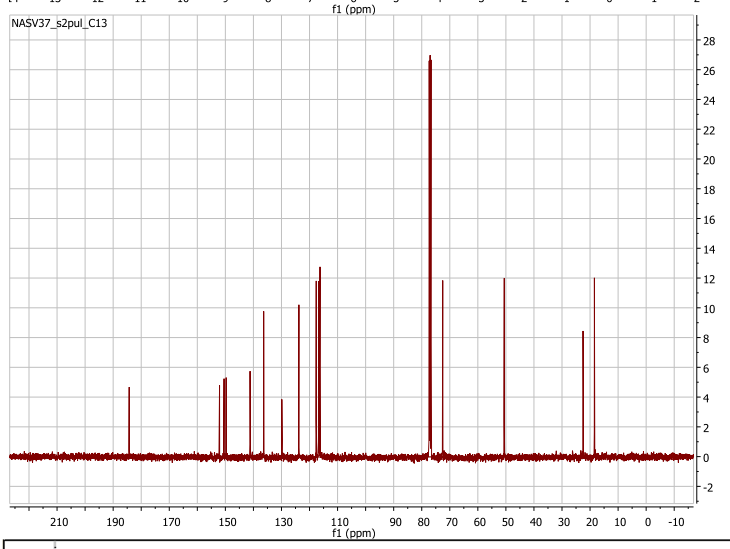

%T
3077.72
2965.34
2926.59
2852.96
1760.17
1748.55
1601.29
1589.67
1562.54
1469.54
1268.03
1047.15
783.64
Wavenumbers (cm-1)

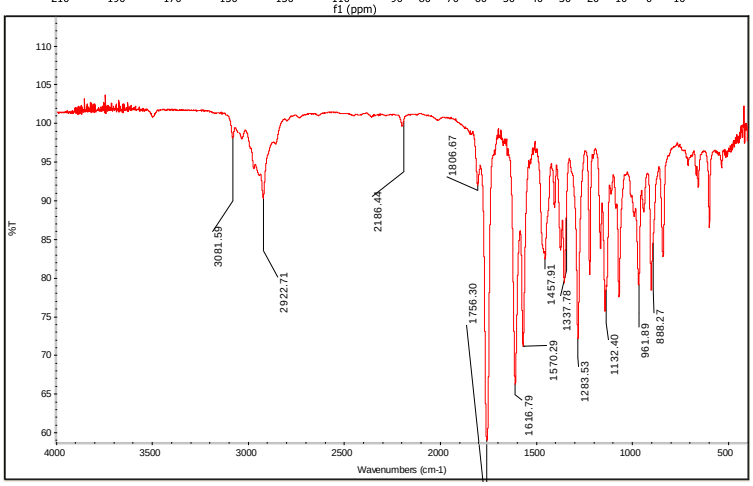

PROTON_01
NASV27
f1 (ppm)

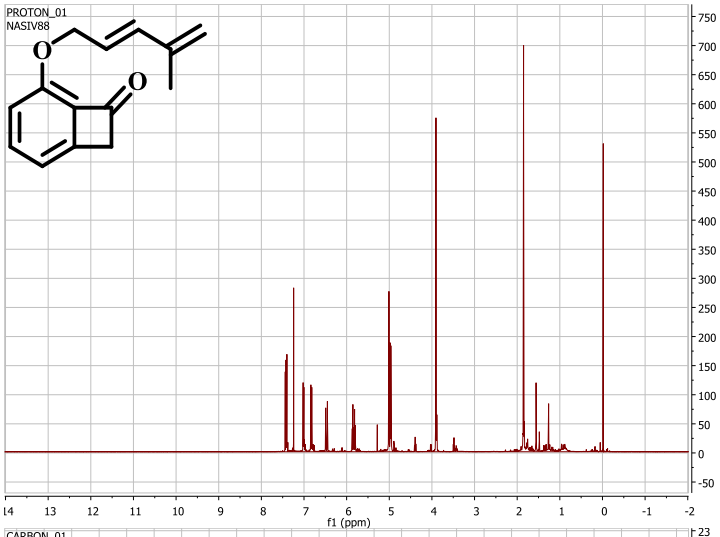

CARBON_01
NASV27
f1 (ppm)

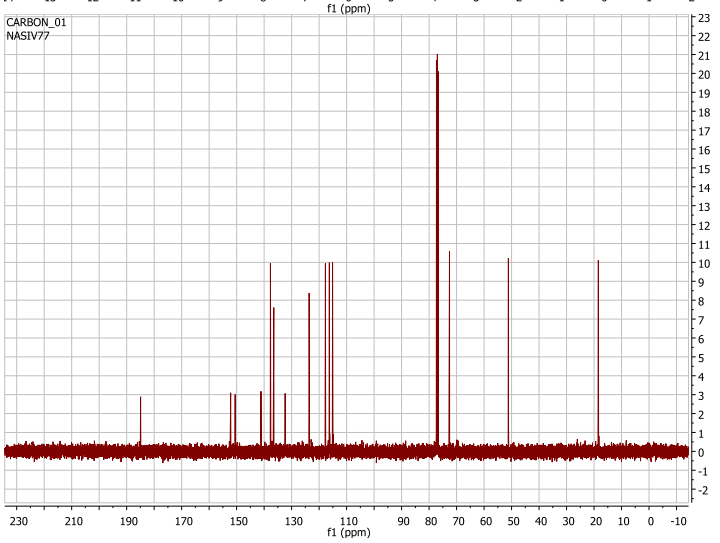

%T
Wavenumbers (cm-1)
2922.05
1764.68
1602.26
1575.04
1474.10
1446.61
1382.35
1269.54
1159.46
1129.82
1050.20
978.02
903.72
784.26
641.22

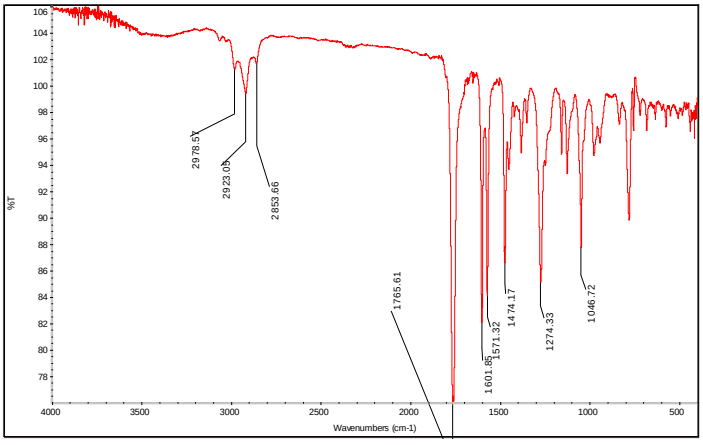

NASV37_s2pul_H1
O
O
f1 (ppm)

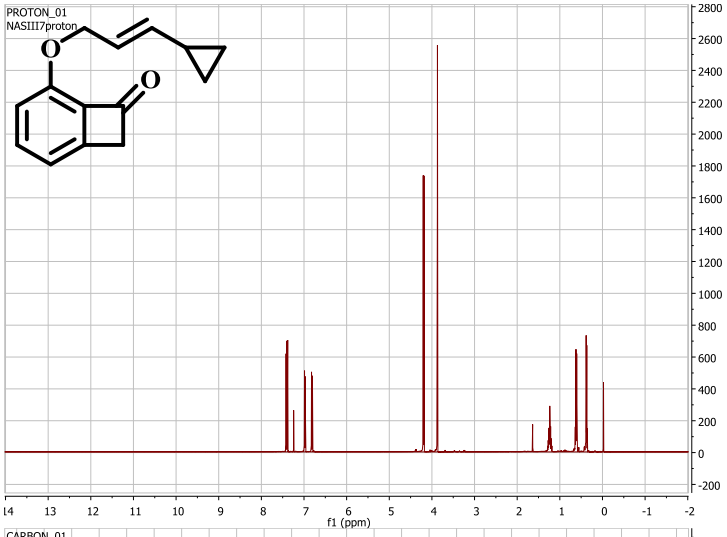

NASV37_s2pul_C13
f1 (ppm)

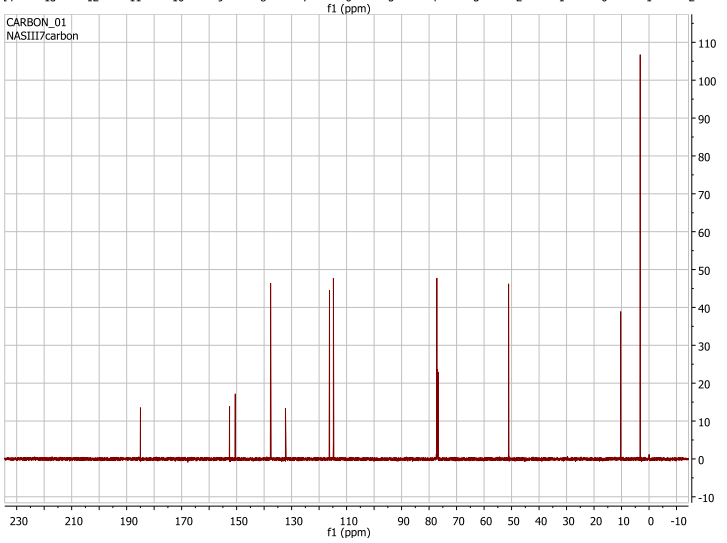

%T
3081.59
2922.71
2186.44
1806.67
1756.30
1616.79
1570.29
1457.91
1337.78
1283.53
1132.40
961.89
888.27
Wavenumbers (cm-1)

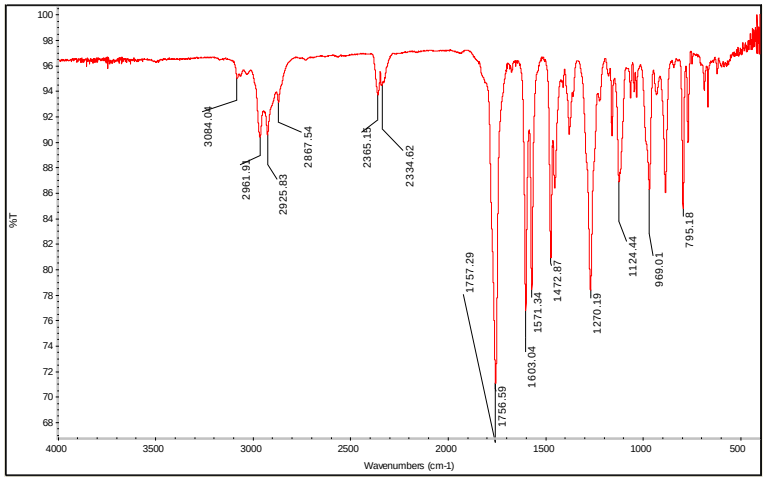

PROTON_01
NASIV88
O
O
f1 (ppm)

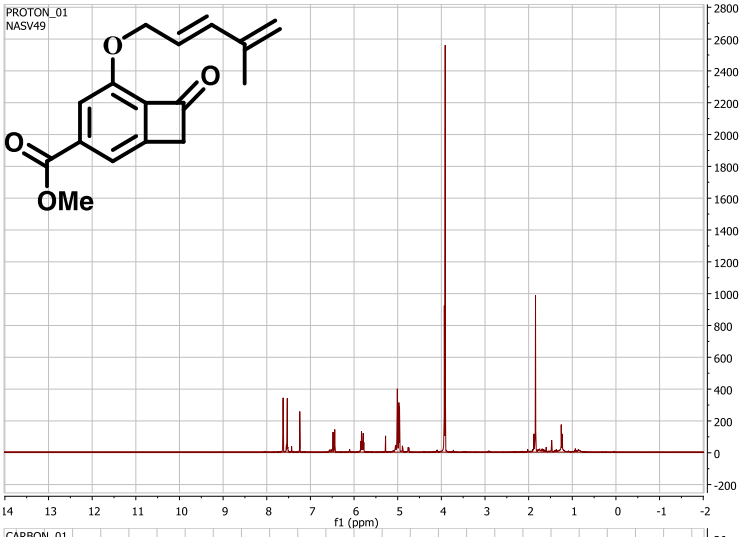

CARBON_01
NASIV77
f1 (ppm)

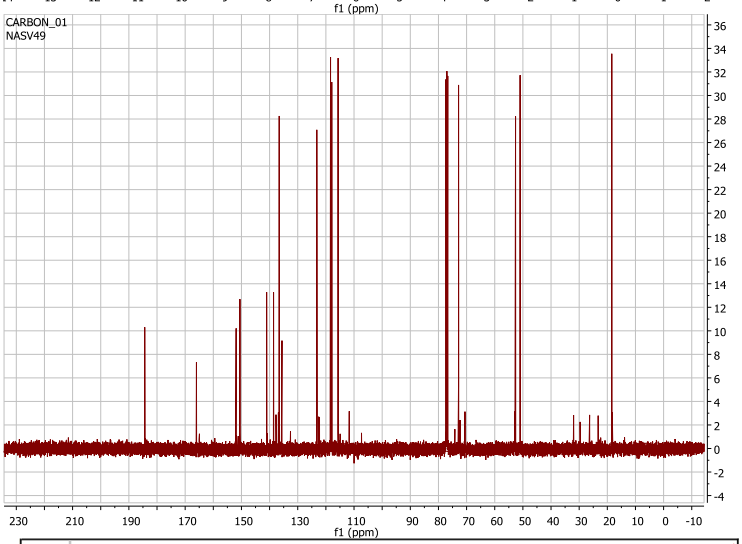

%T
2978.57
2923.05
2853.66
1765.61
1601.85
1571.32
1474.17
1274.33
1046.72
Wavenumbers (cm-1)

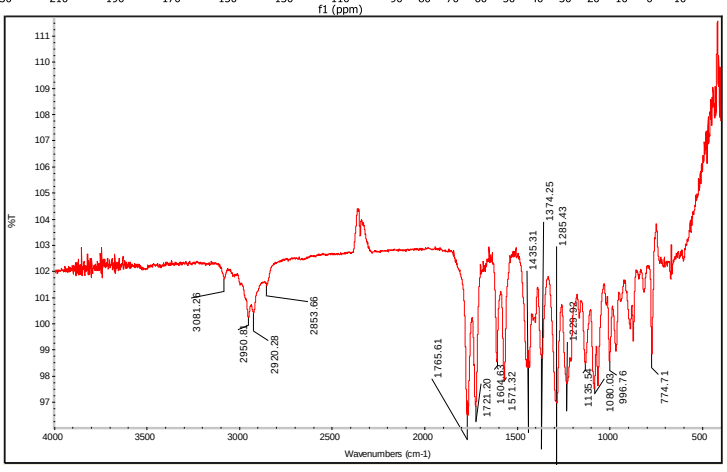

PROTON_01
NASIII7proton
O
O
f1 (ppm)

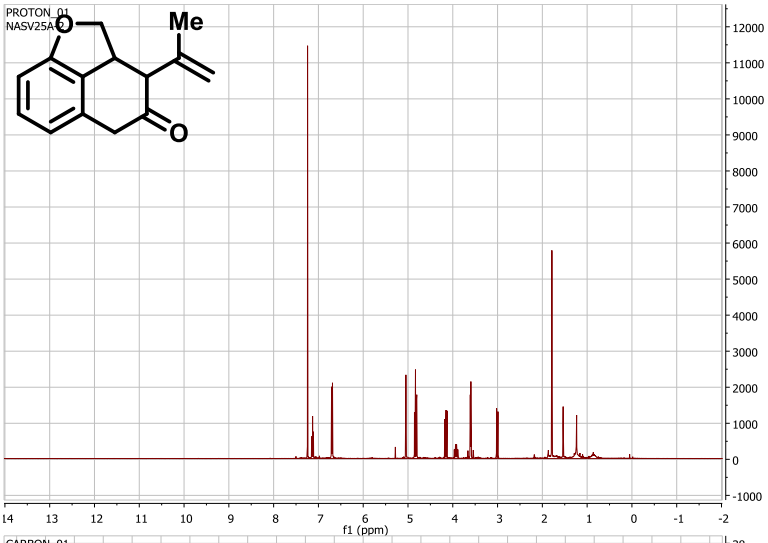

CARBON_01
NASIII7carbon
f1 (ppm)

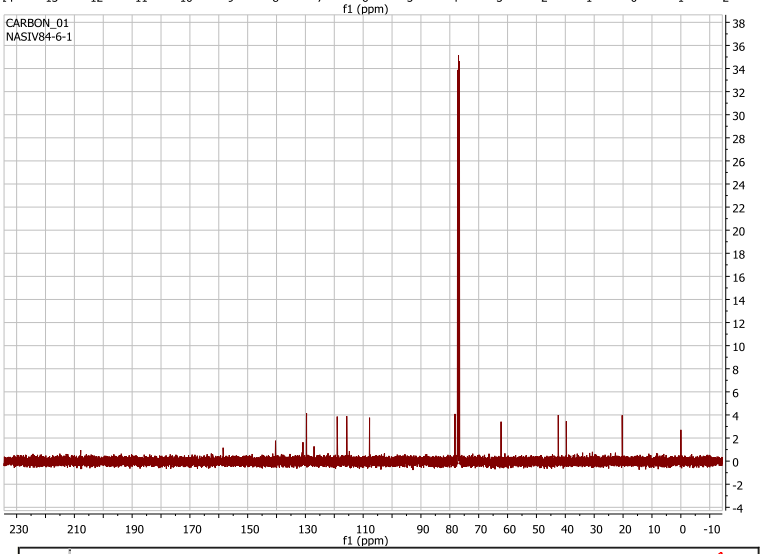

%T
3084.08
2961.91
2925.83
2867.54
2365.15
2334.62
1757.29
1756.59
1603.04
1571.34
1472.87
1270.19
1124.44
969.01
795.18
Wavenumbers (cm-1)

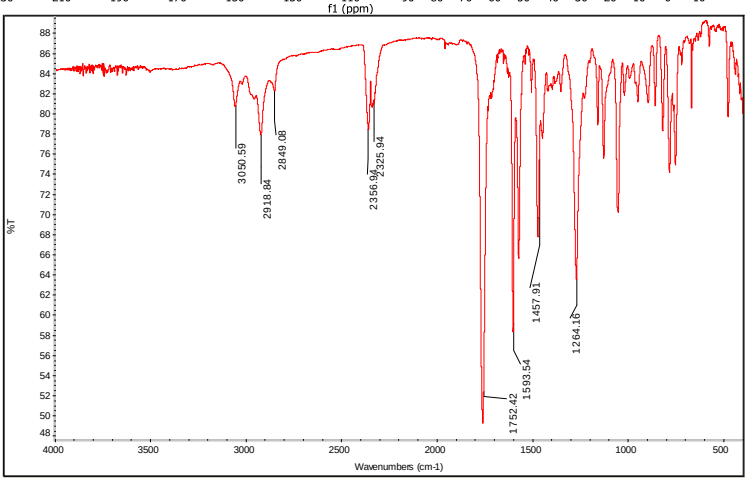

PROTON_01
NASV49
O
O
O
OMe
f1 (ppm)

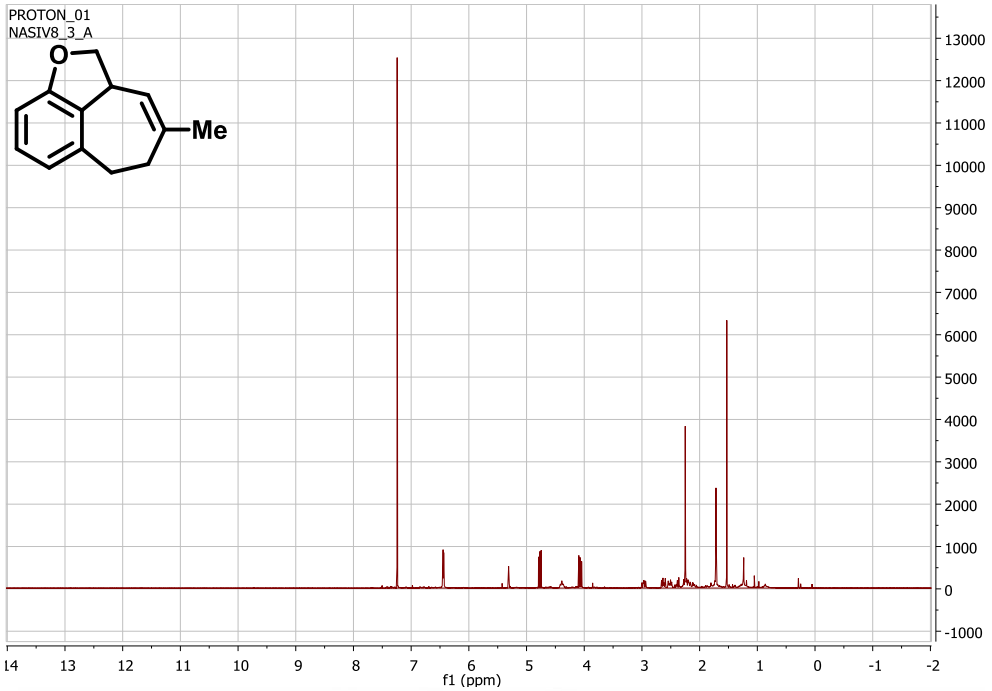

CARBON_01
NASV49
f1 (ppm)

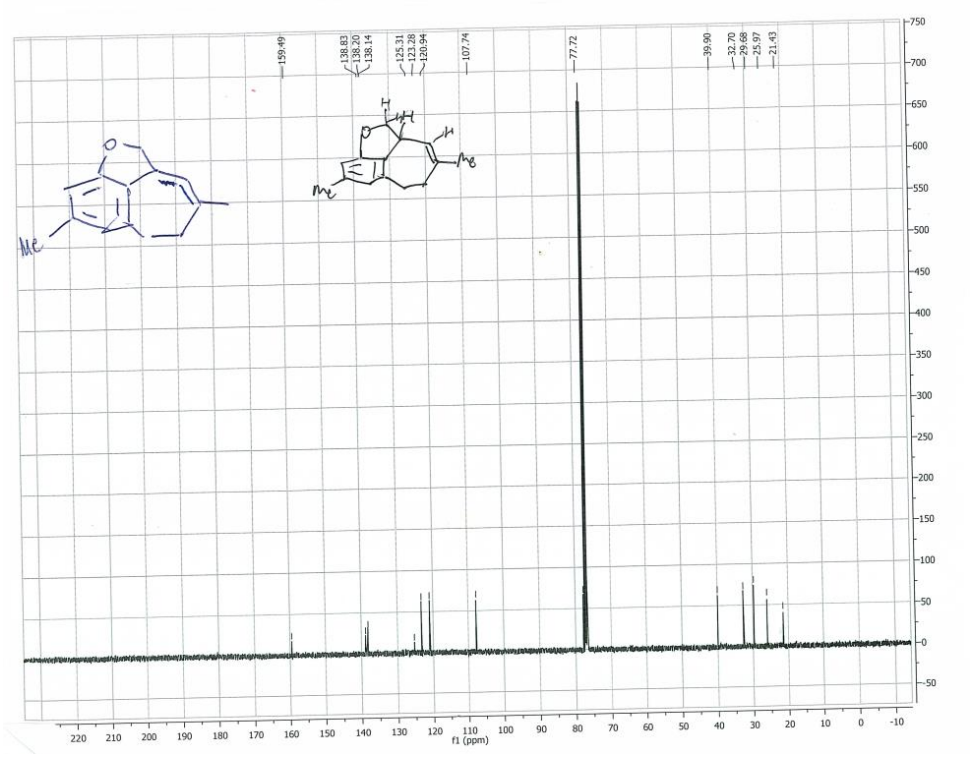

%T
3081.26
2950.81
2920.28
2853.66
1765.61
1721.20
1604.43
1571.52
1435.31
1374.25
1285.43
1229.39
1135.62
1080.00
996.76
774.71
Wavenumbers (cm-1)

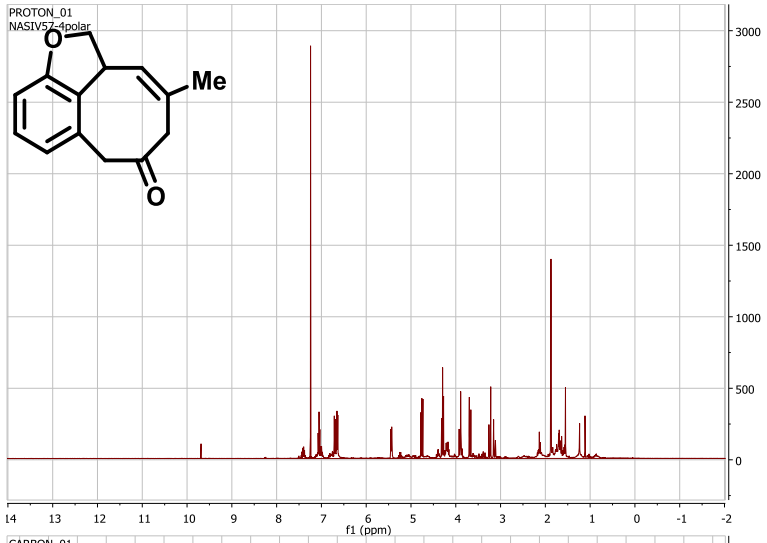

PROTON_01
NASV25A-6
Me
O
O
f1 (ppm)

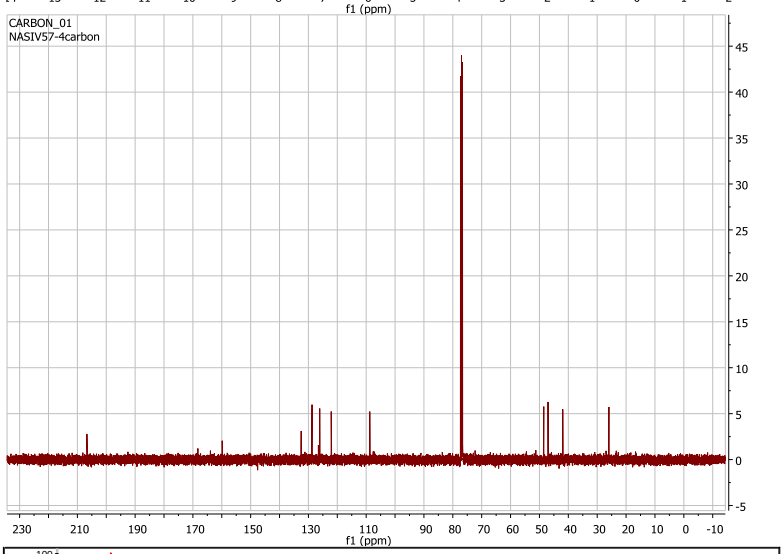

CARBON_01
NASIV84-6-1
f1 (ppm)

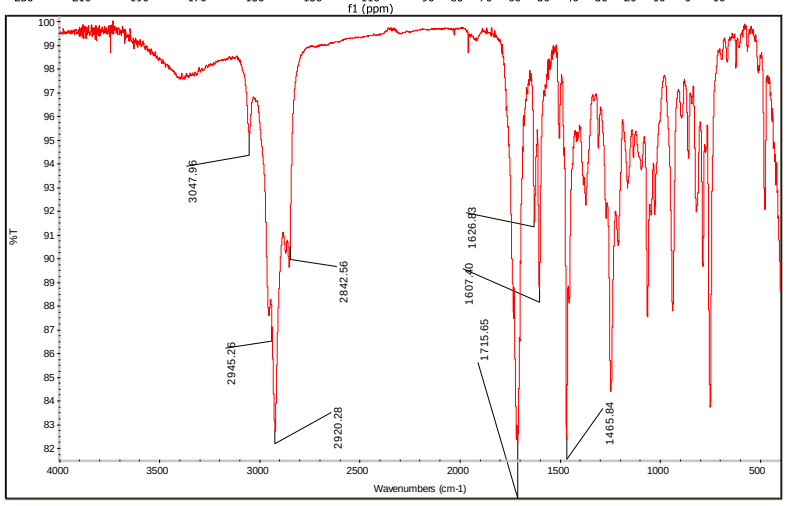

%T
3050.59
2918.84
2849.08
2356.99
2325.94
1752.42
1593.54
1457.91
1264.18
Wavenumbers (cm-1)

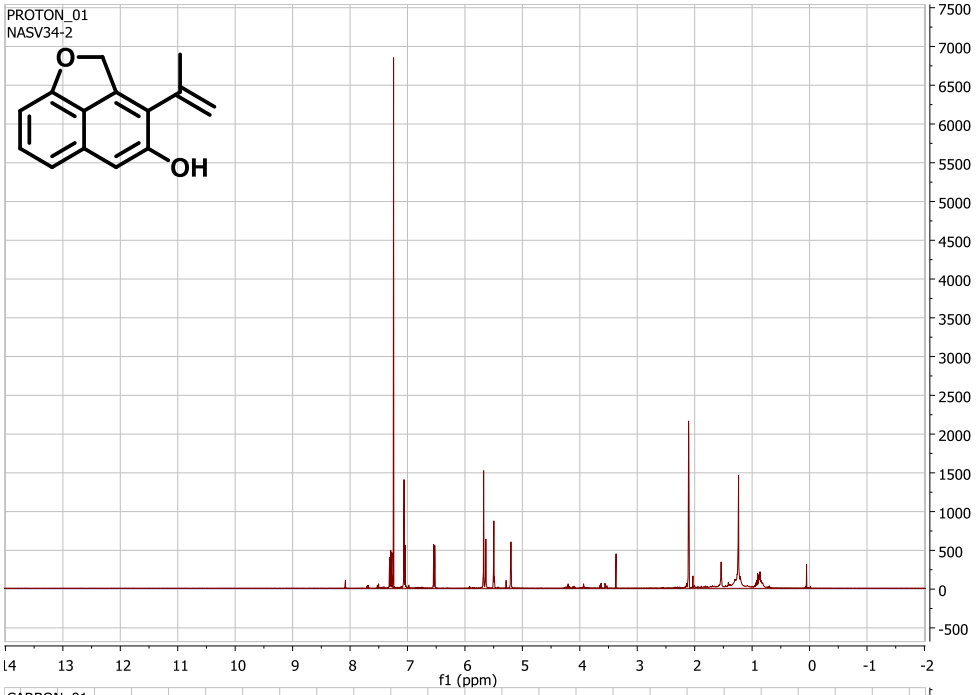

PROTON_01
NASIV8_3_A
O
Me
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2
f1 (ppm)

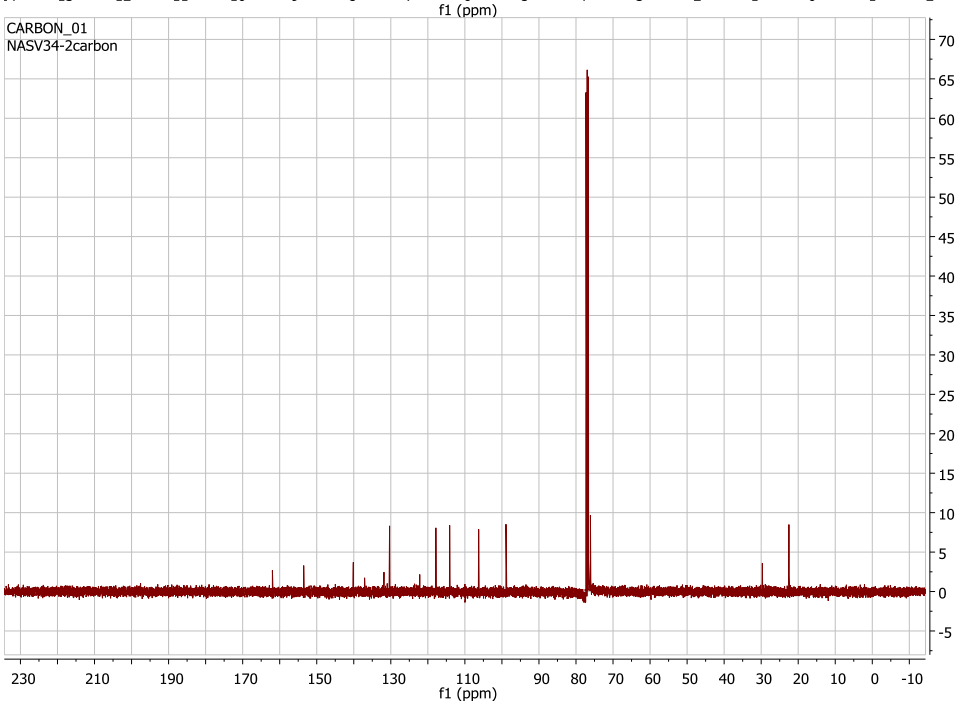

159.49
138.83
138.20
138.14
125.31
123.38
120.94
107.74
77.72
39.90
32.70
29.68
25.97
21.43
O
Me
H
H
H
O
Me
Me
750
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

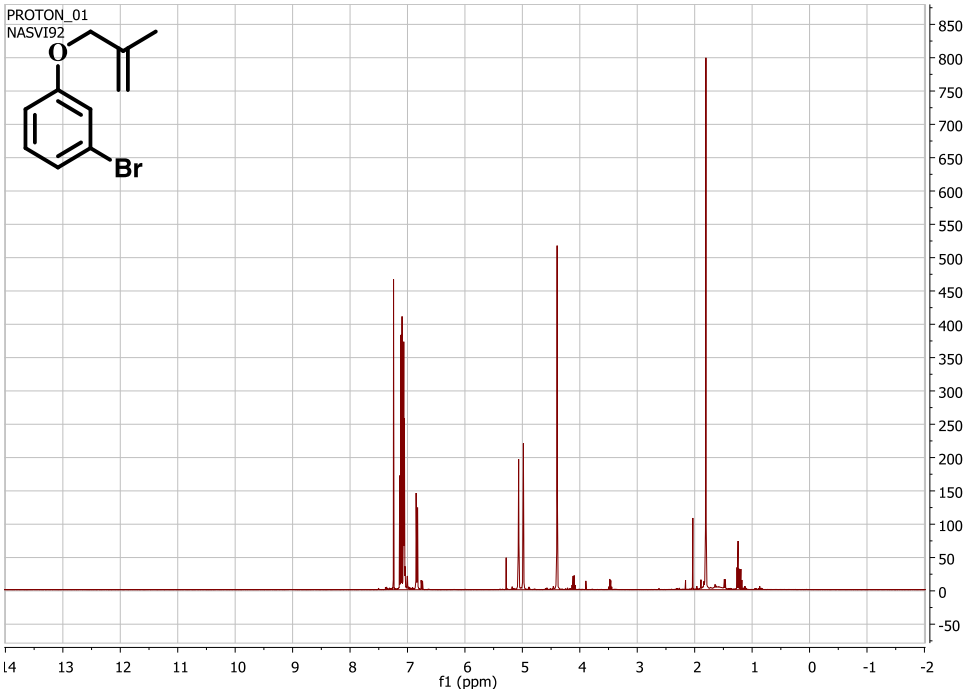

PROTON_01
NASIV57-4polar
O
Me
O
f1 (ppm)

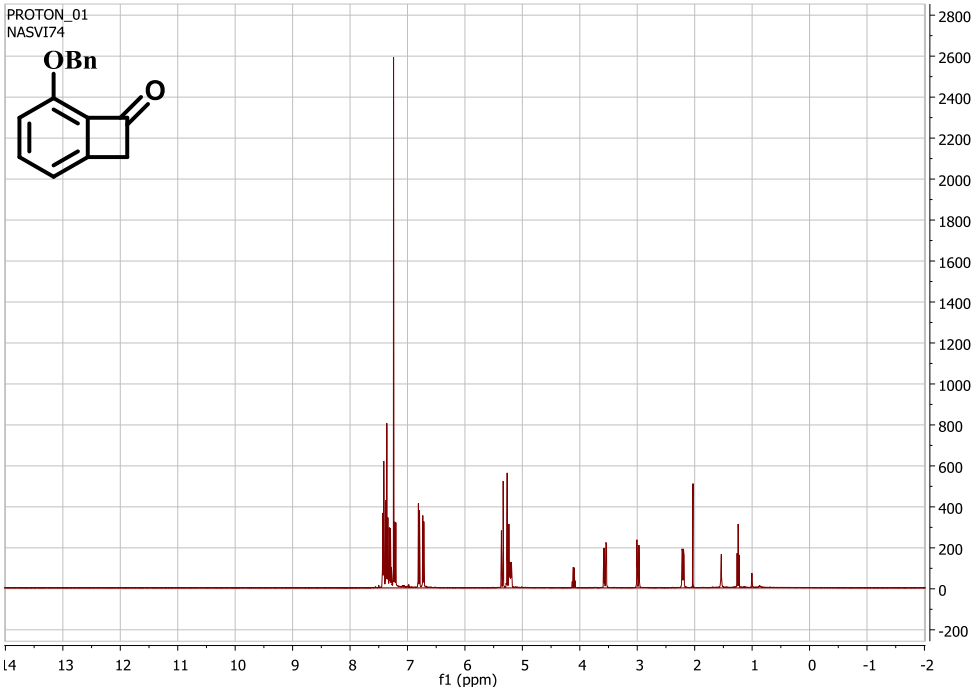

CARBON_01
NASIV57-4carbon
f1 (ppm)

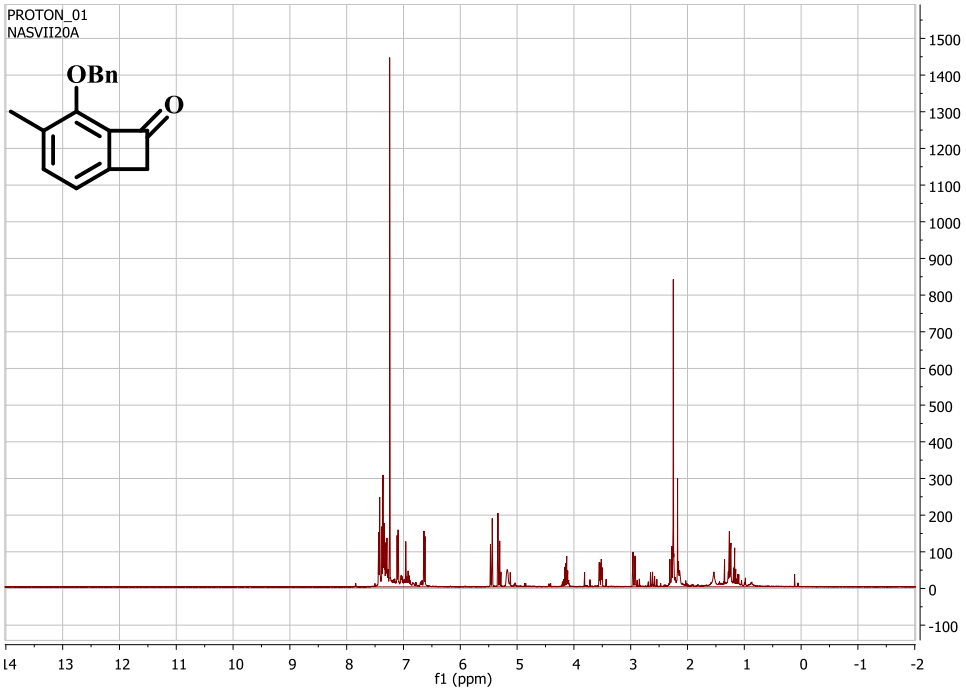

%T
3047.96
2945.26
2920.28
2842.56
1715.65
1607.40
1626.83
1465.84
Wavenumbers (cm-1)


PROTON_01
NASV34-2
O
OH
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2
f1 (ppm)


CARBON_01
NASV34-2carbon
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
-5
230 210 190 170 150 130 110 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


PROTON_01
NASVI92
O
Br
850
800
750
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f1 (ppm)


PROTON_01
NASVI74
OBn
O
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f1 (ppm)


PROTON_01
NASVII20A
OBn
O
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f1 (ppm)

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